No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1	物化	Brown, R P; Delp, M D; Lindstedt, S L; Rhomberg, L R; Beliles, R P	Physiological parameter values for physiologically based pharmacokinetic models	1997	Toxicol Ind Health. 1997 Jul-Aug;13(4):407-84. doi: 10.1177/074823379701300401.	No abstract available			●							-		D	-
2	物化	Martin, J W; Ellis, D A; Mabury, S A; Hurley, M D; Wallington, T J	Atmospheric chemistry of perfluoroalkanesulfonamides: kinetic and product studies of the OH radical and Cl atom initiated oxidation of N ethyl perfluorobutanesulfonamide	2006	Environ Sci Technol. 2006 Feb 1;40(3):864-72. doi: 10.1021/es051362f.	Perfluorooctanesulfonamides [C8F17SO2N(R1)(R2)] are present in the atmosphere and may, via atmospheric transport and oxidation, contribute to perfluorocarboxylates (PFCA) and perfluorooctanesulfonate (PFOS) pollution in remote locations. Smog chamber experiments with the perfluorobutanesulfonyl analogue N-ethyl perfluorobutanesulfonamide [NEtFBSA; C4F9SO2N(H)CH2CH3] were performed to assess this possibility. By use of relative rate methods, rate constants for reactions of NEtFBSA with chlorine atoms (296 K) and OH radicals (301 K) were determined to be kCL) = (8.37 +/- 1.44) x 10(-12) and kOH = (3.74 +/- 0.77) x 10(-13) cm3 molecule(-1) s(-1), indicating OH reactions will be dominant in the troposphere. Simple modeling exercises suggestthat reaction with OH radicals will dominate removal of perfluoroalkanesulfonamides from the gas phase (wet and dry deposition will not be important) and that the atmospheric lifetime of NEtFBSA in the gas phase will be 20-50 days, thus allowing substantial long-range atmospheric transport. Liquid chromatography/tandem mass spectrometry (LC/MS/MS) analysis showed that the primary products of chlorine atom initiated oxidation were the ketone C4F9SO2N(H)COCH3; aldehyde 1, C4F9SO2N(H)CH2CHO; and a product identified as C4F9SO2N(C2H5O)- by high-resolution MS but whose structure remains tentative. Another reaction product, aldehyde 2, C4F9SO2N(H)CHO, was also observed and was presumed to be a secondary oxidation product of aldehyde 1. Perfluorobutanesulfonate was not detected above the level of the blank in any sample; however, three perfluoroalkanecarboxylates (C3F7CO2-, C2F5CO2-, and			●	●						-		B	-
3	物化	3M.	The science of organic fluorochemistry	1999	U.S. Environmental Protection Agency. OPPT-2002-0043-0006. http://www.fluoridealert.org/pesticides/pfos.fr.final.docket.0006.pdf.	No abstract available				●						企業データ		C	-
4	物化	3M.	Screening level human exposure assessment report. 3M Decatur, Alabama facility PFOA site-related environmental monitoring program	2008	3M Decatur, Alabama facility PFOA site-related environmental monitoring program. St. Paul, MN: 3M Company.	No abstract available				●						企業データ		A	-
5	物化	Bhhatarai, Barun; Gramatica, Paola	Prediction of aqueous solubility, vapor pressure and critical micelle concentration for aquatic partitioning of perfluorinated chemicals	2011	Environ Sci Technol. 2011 Oct 1;45(19):8120-8. doi: 10.1021/es101181g. Epub 2010 Oct 19.	The majority of perfluorinated chemicals (PFCs) are of increasing risk to biota and environment due to their physicochemical stability, wide transport in the environment and difficulty in biodegradation. It is necessary to identify and prioritize these harmful PFCs and to characterize their physicochemical properties that govern the solubility, distribution and fate of these chemicals in an aquatic ecosystem. Therefore, available experimental data (10-35 compounds) of three important properties: aqueous solubility (AqS), vapor pressure (VP) and critical micelle concentration (CMC) on per- and polyfluorinated compounds were collected for quantitative structure-property relationship (QSPR) modeling. Simple and robust models based on theoretical molecular descriptors were developed and externally validated for predictivity. Model predictions on selected PFCs were compared with available experimental data and other published in silico predictions. The structural applicability domains (AD) of the models were verified on a bigger data set of 221 compounds. The predicted properties of the chemicals that are within the AD, are reliable, and they help to reduce the wide data gap that exists. Moreover, the predictions of AqS, VP, and CMC of most common PFCs were evaluated to understand the aquatic partitioning and to derive a relation with the available experimental data of bioconcentration factor (BCF).				●						-	1	A	-
6	物化	ChemIDplus	Perfluoroalkyls	2020	ChemIDplus. Bethesda, MD: U.S. National Library of Medicine.	No abstract available				●						ChemIDplus		D	-
7	物化	EPA.	Draft risk assessment of the potential human health effects associated with exposure to perfluorooctanoic acid and its salts	2005	U.S. Environmental Protection Agency. https://www.fluoridealert.org/wp-content/pesticides/2005/epa.draft.risk.jan.2005.pdf	No abstract available				●		●				評価書		A	-
8	物化	EPA.	Perfluoroalkyls	2021	Substance registry system. U.S. Environmental Protection Agency.	No abstract available				●						評価書		D	-
9	物化	EPA.	Health effects document for perfluorooctanoic acid (PFOA)	2014	U.S. Environmental Protection Agency,EPA-822-R-14-001, https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P100IRZ1.txt	No abstract available				●						評価書		A	-
10	物化	Goss, Kai-Uwe	The pKa values of PFOA and other highly fluorinated carboxylic acids	2008	Environ Sci Technol. 2008 Jan 15;42(2):456-8. doi: 10.1021/es702192c.	The dissociated and nondissociated species of any organic acid differ largely in their physicochemical behavior. The ratio of both species in aqueous systems is determined by the respective pKa value. For perfluorooctanoic acid recent fate-modeling studies have applied a pKa value of 2.8. This value likely is too high by 3 log units. Here, the correct value is estimated to be close to -0.5 based on analogy considerations and molecular modeling. Calculated pKa values for other highly fluorinated carboxylic acids are also presented.				●		●				-	1	A	-
11	物化	HSDB.	Perfluoroheptanoic acid	2019	Hazardous Substances Data Bank. National Library of Medicine.	No abstract available				●						HSDB		B	-
12	物化	Inoue, Yoshiyuki; Hashizume, Naoki; Yakata, Naoaki; Murakami, Hidekazu; Suzuki, Yasuyuki; Kikushima, Erina; Otsuka, Masanori	Unique physicochemical properties of perfluorinated compounds and their bioconcentration in common carp Cyprinus carpio L	2012	Arch Environ Contam Toxicol. 2012 May;62(4):672-80. doi: 10.1007/s00244-011-9730-7. Epub 2011 Nov 30.	Carp (Cyprinus carpio L.) was exposed to perfluorinated compounds (PFCs)-perfluoroalkyl carboxylic acids (number of carbon atoms, C = 8, 11, 12, 14, 16, and 18) and perfluorooctane sulfonate (PFOS)-in bioconcentration tests to compare the bioconcentration factors (BCFs) and physicochemical properties of each specific compound. Despite having the same number of carbon atoms (C = 8), the BCFs of perfuloroctanoic acid (PFOA) and PFOS differed by more than two orders of magnitude (PFOA BCF = < 5.1 to 9.4; PFOS BCF = 720 to 1300). The highest BCFs were obtained from perfluorododecanoic acid (BCF = 10,000 to 16,000) and perfluorotetradecanoic acid (BCF = 16,000 to 17,000). The longest observed depuration half-lives were for perfluorohexadecanoic acid (48 to 54 days) and PFOS (45 to 52 days). The concentrations of PFCs were highest in the viscera, followed by the head, integument, and remaining parts of the test fish. PFCs concentrations in the integument, which was in direct contact with the test substances, were relatively greater than that of other lipophilic substance (hexachlorobenzene). It is likely that Clog P would be a better parameter than log K (ow) for the prediction of BCFs for PFCs. Threshold values for PFCs bioaccumulation potential (molecular weight = 700, maximum diameter = 2 nm) seemed to deviate from those generally reported because of the specific steric bulk effect of molecule size.				●						-		B	-
13	物化	Mary A. Kaiser, Barbara S. Larsen, Chien-Ping C. Kao, and Robert C. Buck	Vapor pressures of perfluoro-octanoic, -nonanoic, -decanoic, -undecanoic, and -dodecanoic acids	2005	J. Chem. Eng. Data 2005, 50, 6, 1841–1843, doi: 10.1021/je050070r	A dynamic method was used to determine the vapor pressures of perfluorooctanoic, -nonanoic, -decanoic, -undecanoic, and -dodecanoic acids. Measurements were made over the temperature range from (59.25 to 190.80) ° C for perfluorooctanoic acid, from (99.63 to 203.12) °C for perfluorononanoic acid, from (129.56 to 218.88) °C for perfluorodecanoic acid, from (112.04 to 237.65) °C for perfluoroundecanoic acid, and from (127.58 to 247.36) °C for perfluorododecanoic acid. Pressures ranged from (0.128 to 96.50) kPa for perfluorooctanoic acid, from (1.12 to 99.97) kPa for perfluorononanoic acid, from (3.129 to 99. 97) kPa for perfluorodecanoic acid, from (0.616 to 99.97) kPa for perfluoroundecanoic acid, and from (0.856 to 99.96) kPa for perfluorododecanoic acid. A sealed vial experiment demonstrated that perfluorooctanoic acid sublimes at room temperature.				●						-		B	-
14	物化	E. A. Kauck and A. R. Diesslin	Some properties of perfluorocarboxylic acids	1951	Ind. Eng. Chem. 1951, 43, 10, 2332–2334, doi: 10.1021/ie50502a044	During an investigation of the electrochemical fluorination of organic compounds dissolved in anhydrous hydrogen fluoride, it was discovered that fully fluorinated acyl fluorides were produced which hydrolyze readily to the corresponding perfluoro acids. Boiling points and liquid densities are presented for the following acids: perfluoriacetic acid, perfluoropropionic acid, perfluorobutyric acid, perfluoroisobutyric acid, perfluorovaleric acid, perfluorocaproic acid, perfluoroheptanoic acid, perfluorocaprylic acid, perfluorocyclohexanecarboxylic acid, and perfluorocyclohexaneacetic acid. With the exception of the first three compounde listed, these substanes are reported for the first time. Data are presented on vapor pressure, viscosity, pH, and equivalent conductance of perfluproacetic and perfluorobutyric acids. A feasible method of preparing a new series of fluorinated acids has been developed and these fluorinated acids are being made available to the chemical public. A wide variety of useful derivatives can be made from these acids. Interest in the acids and their derivatives is expected because of their unusual chemical and physical properties.				●						アブスト追記		B	-
15	物化	Kroschwitz JI, Howe-Grant M.	Perfluorooctanoic	1994	Kirk-Othmer encyclopedia of chemical toxicology. 4th ed. Vol. 11. New York, NY: John Wiley & Sons, Inc., 551.	No abstract available				●						書籍		D	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ランク①	文献ランク②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
16	物化	Krusic, Paul J; Roe, D Christopher	Gas-phase NMR technique for studying the thermolysis of materials: Thermal decomposition of ammonium perfluorooctanoate	2004	Anal Chem. 2004 Jul 1;76(13):3800-3. doi: 10.1021/ac049667k.	The kinetics of the thermal decomposition of ammonium perfluorooctanoate (APFO) has been studied by high-temperature gas-phase nuclear magnetic resonance spectroscopy over the temperature range 196-234 degrees C. We find that APFO cleanly decomposes by first-order kinetics to give the hydrofluorocarbon 1-H-perfluoroheptane and is completely decomposed (>99%) in a matter of minutes at the upper limit of this temperature range. Based on the temperature dependence of the measured rate constants, we find that the enthalpy and entropy of activation are DeltaH++ = 150 +/- 11 kJ mol(-1) and DeltaS++ = 3 +/- 23 J mol(-)(1) deg(-1). These activation parameters may be used to calculate the rate of APFO decomposition at the elevated temperatures (350-400 degrees C) at which fluoropolymers are processed; for example, at 350 degrees C the half-life for APFO is estimated to be less than 0.2 s. Our studies provide the fundamental parameters involved in the decomposition of the ammonium salt of perfluorooctanoic acid and indicate the utility of gas-phase NMR for thermolysis studies of a variety of materials that release compounds that are volatile at the temperature of decomposition and that contain an NMR-active nucleus.				●						-		C	-
17	物化	Paul J. Krusic; Alexander Marchione Chemours; D. Christopher Roe	Gas-phase NMR studies of the thermolysis of perfluorooctanoic acid	2005	Journal of Fluorine Chemistry. 126(11):1510-1516, DOI:10.1016/j.jfluchem.2005.08.016	The thermolysis of perfluorooctanoic acid (CF3(CF2)6COOH) has been studied kinetically by high-temperature gas-phase NMR in both sodium borosilicate glass and quartz ampoules. In both cases, 1-H-perfluoroheptane is the major product, but the decomposition is considerably slower in quartz. The decomposition in borosilicate ampoules at 307°C is greatly accelerated by the presence of crushed borosilicate glass and the reaction appears to be completely heterogeneous. Perfluoro-1-heptene is produced as a minor product and time-of-flight secondary ion mass spectrometry (ToF-SIMS) examination of the inner surface of the borosilicate glass ampoule after reaction reveals the presence of NaF. The thermolysis in quartz ampoules was studied by ex situ heating in the temperature range 355–385°C and produced moderate amounts of perfluoro-1-heptene and SiF4 in addition to 1-H-perfluoroheptane. Thermolysis in the presence of added crushed quartz accelerates the decomposition, as does increasing the concentration of perfluorooctanoic acid or carrying out the thermolysis in the presence of water. The thermolysis of perfluorooctanoic acid thus proceeds at widely different rates depending on concentration and on the physical and chemical environment. By contrast, the pyrolysis of ammonium perfluorooctanoate is more facile by orders of magnitude and proceeds by first-order kinetics at essentially the same rates in both quartz and borosilicate ampoules with an estimated half-life of 2s at 307°C.				●						-		C	-
18	物化	Kunieda, H.; Shinoda, K.	Krafft points, critical micelle concentrations, surface tension, and solubilizing power of aqueous solutions of fluorinated surfactants	1976	J. Phys. Chem. 1976, 80, 22, 2468–2470, doi: 10.1021/j100563a007	The Krafft points, critical micelle Concentrations (cmc), surface tension above the cmc, and solubilizing power in aqueous solutions of perfluoroalkane carboxylates as functions of fluorocarbon chain length and the types of gegenions have been studied. The Krafft point, surface tension above the cmc, and solubilizing power differ markedly with the types of gegenions, but the cmc is mainly dependent on the fluorocarbon chain length and not on the types of gegenions of same valency.				●						-	1	A	-
19	物化	W. C. Kwan	Physical property determination of perfluorinated surfactants A thesis submitted in conformity with the requirements for the degree of Masters of Science in Environmental Chemistry, Graduate Department of Chemistry, University of Toronto	2001	Available online at https://9doc.org/document/z1dlwexe-physical-property-determination-of-perfluorinated-surfactants.html	No abstract available				●					-		D	-
20	物化	Lide DR.	Pentadecafluorooctanoic acid, nondecafluorodecanoic acid, and heptafluorobutanoic acid	2005	In: CRC handbook of chemistry and physics. 86th ed. Boca Raton, FL: Taylor and Francis, 3-412, 3-372, 3-398.	No abstract available				●					書籍		B	-
21	物化	McGuire, Meghan E; Schaefer, Charles; Richards, Trenton; Backe, Will J; Field, Jennifer A; Houtz, Erika; Sedlak, David L; Guelfo, Jennifer L; Wunsch, Assaf; Higgins, Christopher P	Evidence of remediation-induced alteration of subsurface poly- and perfluoroalkyl substance distribution at a former firefighter training area	2014	Environ Sci Technol. 2014 Jun 17;48(12):6644-52. doi: 10.1021/es5006187. Epub 2014 Jun 9.	Poly- and perfluoroalkyl substances (PFASs) are a class of fluorinated chemicals that are utilized in firefighting and have been reported in groundwater and soil at several firefighter training areas. In this study, soil and groundwater samples were collected from across a former firefighter training area to examine the extent to which remedial activities have altered the composition and spatial distribution of PFASs in the subsurface. Log Koc values for perfluoroalkyl acids (PFAAs), estimated from analysis of paired samples of groundwater and aquifer solids, indicated that solid/water partitioning was not entirely consistent with predictions based on laboratory studies. Differential PFAA transport was not strongly evident in the subsurface, likely due to remediation-induced conditions. When compared to the surface soil spatial distributions, the relative concentrations of perfluorooctanesulfonate (PFOS) and PFAA precursors in groundwater strongly suggest that remedial activities altered the subsurface PFAS distribution, presumably through significant pumping of groundwater and transformation of precursors to PFAAs. Additional evidence for transformation of PFAA precursors during remediation included elevated ratios of perfluorohexanesulfonate (PFHxS) to PFOS in groundwater near oxygen sparging wells.				●						-		B	-
22	物化	Patricia M. Savu	Fluorinated higher carboxylic acids	2000	Kirk-Othmer Encyclopedia of Chemical Technology, doi: 10.1002/0471238961.0612211519012221.a01	Perfluorinated carboxylic acids are corrosive liquids or solids. The acids are completely ionized in water. The acids are of commercial significance because of their unusual acid strength, chemical stability, high surface activity, and salt solubility characteristics. The higher members of the series have the property of decreasing the surface tension of aqueous solutions well below the point possible with any type of hydrocarbon surfactant. There are five methods for the preparation of long-chain perfluorinated carboxylic acids and derivatives: electrochemical fluorination, direct fluorination, telomerization of tetrafluoroethylene, oligomerization of hexafluoropropylene oxide, and photooxidation of tetrafluoroethylene and hexafluoropropylene. In general, the reactions of the perfluoroacids are similar to those of the hydrocarbon acids, although in some cases the electronegativity of the perfluoroalkyl groups make formation of certain derivatives easier or harder. A general summary of formation and properties of the derivatives of perfluorinated acids is discussed. Data on the fluorinated dicarboxylic acids and their derivatives are also summarized.				●						-		C	-
23	物化	Siegemund G, Schwertfeger W, Feiring A, et al.	Fluorine compounds, organic	2016	ULLMANN'S Encyclopedia of Industrial Chemistry, doi: 10.1002/14356007.a11_349.pub2	No abstract available				●					-		D	-
24	物化	SPARC.	Macroscopic pKa	2008	Sparc Performs Automated Reasoning in Chemistry.	No abstract available				●					SPAC、要確認？		D	-
25	物化	Vierke, Lena; Berger, Urs; Cousins, Ian T	Estimation of the acid dissociation constant of perfluoroalkyl carboxylic acids through an experimental investigation of their water-to-air transport	2013	Environ Sci Technol. 2013 Oct 1;47(19):11032-9. doi: 10.1021/es402691z. Epub 2013 Sep 10.	The acid dissociation constants (pKas) of perfluoroalkyl carboxylic acids (PFCAs) have been the subject of discussion in the literature; for example, values from -0.2 to 3.8 have been suggested for perfluorooctanoic acid (PFOA). The dissociated anionic conjugate bases of PFCAs have negligible air-water partition coefficients (KAWs) and do not volatilize from water. The neutral acids, however, have relatively high KAWs and volatilization from water has been demonstrated. The extent of volatilization of PFCAs in the environment will depend on the water pH and their pKa. Knowledge of the pKas of PFCAs is therefore vital for understanding their environmental transport and fate. We investigated the water-to-air transfer of PFCAs in a novel experimental setup. We used ~1 μg L(-1) of PFCAs in water (above environmental background concentrations but below the concentration at which self-association occurs) at different water pH (pH 0.3 to pH 6.9) and sampled the PFCAs volatilized from water during a 2-day experiment. Our results suggest that the pKas of C4-11 PFCAs are <1.6. For PFOA, we derived a pKa of 0.5 from fitting the experimental measurements with a volatilization model. Perfluoroalkane sulfonic acids were not volatilized, suggesting that their pKas are below the investigated pH range (pKa <0.3).				●						-	1	A	-
26	物化	Xiang, Qian; Shan, Guoqiang; Wu, Wei; Jin, Hangbiao; Zhu, Lingyan	Measuring log Kow coefficients of neutral species of perfluoroalkyl carboxylic acids using reversed-phase high-performance liquid chromatography	2018	Environ Pollut. 2018 Nov;242(Pt B):1283-1290. doi: 10.1016/j.envpol.2018.08.009. Epub 2018 Aug 8.	Accurate measuring n-octanol/water partition coefficients (log K(ow)) of perfluoroalkyl carboxylic acids (PFCAs) using experimental approach has been proven to be very difficult due to their special properties. The ionizable carboxyl groups in PFCAs make their log K(ow) dependent on pH. In this study, the log K(ow) values of neutral species of PFCAs (C(4≤n≤14)) were measured based on reversed-phase high-performance liquid chromatography (RP-HPLC) with the mobile phase pH varying in the range of 1.09-5.00. The relationship between log K(ow) and retention times was established using some reference compounds (including agrochemicals, polycyclic aromatic hydrocarbons) with known log K(ow) values, and then validated with alkyl fatty acids, which have similar chemical structures as PFCAs. The apparent log K(ow) (i.e., log D(ow)) of the C(4-14) PFCAs were calculated based on their retention times using the established model, and they displayed a negative linear relationship with the mobile phase pH in the range of 1.09-4.00. Consequently, the log D(ow) values were converted to the corresponding log K(ow) values (1.05-7.19) based on the relationship of log D(ow) = log K(ow) + pK(a) - pH. The log K(ow) increased with perfluorinated carbon chain length with a greater rate for C(4) to C(5) PFCAs than for C(5-14) PFCAs.				●						-	1	A	-
27	物化	Zhao, Y G; Wan, H T; Wong, M H; Wong, Chris K C	Partitioning behavior of perfluorinated compounds between sediment and biota in the Pearl River Delta of South China	2014	Mar Pollut Bull. 2014 Jun 15;83(1):148-54. doi: 10.1016/j.marpolbul.2014.03.060. Epub 2014 Apr 26.	Surface sediment and biota were collected from 12 sampling sites - seven along the Pearl River Delta and five along the Hong Kong coastline. Perfluorinated compound (PFC) concentrations were detected using a high-performance-liquid-chromatogram-tandem-mass-spectrometry system. Analytical results indicated that the total PFC concentrations were in the range of 0.15-3.11 ng/g dry weight in sediments, while the total PFC concentrations in oyster and mussel samples were between 0.46-1.96 and 0.66-3.43 ng/g wet weight, respectively. The major types of PFCs detected in the sediment samples were perfluorooctanesulfonic acid (PFOS) and perfluorobutanoic acid (PFBA), with concentrations ranging from low limits of quantification to 0.86±0.12 ng/g dry weight and 1.50±0.26 ng/g dry weight, respectively. In bivalve samples, PFOS was the dominant contaminant with concentrations ranging from 0.25±0.09 to 0.83±0.12 ng/g wet weight in oysters and 0.41±0.14 to 1.47±0.25 ng/g wet weight in mussels. An increase in PFC concentration was found to be correlated with increased human population density in the study areas.				●						-		C	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献ランク①	文献ランク②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
28	物化	Tang, C. Y.; Kwon, Y. N.,am; Leckie, J. O.	Effect of membrane chemistry and coating layer on physiochemical properties of thin film composite polyamide RO and NF membranes I	2009	Desalination. Volume 242, Issues 1–3, June 2009, Pages 149-167, doi: 10.1016/j.desal.2008.04.003	The physiochemical properties of reserve osmosis (RO) and nanofiltration (NF) polyamide (PA) membranes are largely determined by their PA chemistry and coatings, if any. Knowledge on such inherent relationship is critically needed in advancing membrane technology. This paper presents a consistent and in-depth characterization on diagnosing the chemistry of polyamide and the presence of any coating or modifying agent. Fourier-transform infrared (FTIR) and x-ray photoelectron spectra (XPS) of 17 commonly used commercial thin film composite polyamide RO and NF membranes are presented. The FTIR spectra for fully aromatic trimesoyl chloride and 1,3-benzenediamine based membranes had an amide II band (1541 cm − 1) and an aromatic amide band (1609 cm − 1) that were absent for the semi-aromatic membranes. Consistent with that, the XPS binding energy shift for carbon atoms in fully aromatic amide groups was higher than that for semi-aromatic ones likely due to the more electron withdrawing environment. An additional intermediate peak with a binding energy shift of 1.1–1.6 eV was present in the XPS spectra of C(1s) for some commercial RO and NF membranes. The additional peak, coupled with FITR analysis over the high wave number region and XPS elemental analysis, provided consistent evidence that these membranes were either coated with an additional coating layer or had a modified PA chemistry.					●							-		D	-
29	物化	Benskin, Jonathan P; De Silva, Amila O; Martin, Jonathan W	Isomer profiling of perfluorinated substances as a tool for source tracking: a review of early findings and future application	2010	Rev Environ Contam Toxicol. 2010;208:111-60. doi: 10.1007/978-1-4419-6880-7_2.	The two major manufacturing techniques for perfluorochemicals can be distinguished based on the isomeric profile of their products. ECF (major use from 1950s to 2002) results in a product containing both linear and branched isomers, while telomerization (major use from 2002 to present) typically yields an isomerically pure, linear product. Among the most important question today, which has implication for future regulation of these chemicals, is to what extent human and environmental exposure is from historical products (i.e., ECF) versus currently manufactured fluorochemicals (i.e., telomer). Perfluoroalkyl-chain branching can also affect the physical and chemical properties of these chemicals, which may influence their environmental transport and degradation, partitioning, bioaccumulation, pharmacokinetics, and toxicity. Unless perfluorinated substances are considered as individual isomers, much of this information will be overlooked or missed altogether, which could potentially lead to inaccuracies in human and environmental risk assessments. In this review, we have highlighted novel findings, current knowledge gaps, and areas for improvement based on early experiments on the disposition of PFA and PFA-precursor isomers in the environment. We have also emphasized the wealth of information that can potentially be gleaned from future work in this area, which renders routine adoption of isomer-specific methodologies an attractive and logical next step in the progression of fluorochemicals analysis. However, despite vast improvements in recent years, a fast and comprehensive method capable of separating all major PFA and PFA-precursor isomers, while removing interferences is still required before these methods becomes routine in most labs. Purified and characterized standards of PFOA and PFOS that have isomer profiles consistent with those of historically produced (i.e., 3M) PFOS and PFOA are also required. The limited data available on PFA isomer profiles that exist in the environment and the biological properties of each isomer suggest that examination of isomer profiles may yield clues on the source of PFA contamination to human and the environment. For example, contributions from historical versus current PFOA emissions can be quantified by examining the isomer profile in abiotic samples . Similarly, residual PFOS/PFOA in pre-2002 consumer products may be distinguished from directly emitted PFOS/PFOA by the existence of slight difference in isomer profile. PFOS signatures may also have the potential to distinguish between indirect exposure (via precursors) versus direct exposure (via the sulfonate), based on findings of isomer-specific and/or enantiospecific biotransformation in vitro. Isomer-specific monitoring extended to longer-chain PFAs may also be informative in determining current and historical exposure sources. Finally, given the recent increase of production of PFOSF-based chemicals, following their 2002 phase out, the ability of using isomer profiles to distinguish between historical and currently produced PFOS may also be possible.						●					-		D	-
30	物化	Lide, D.R.	CRC Handbook of Chemistry and Physics	2003	CRC Handbook of Chemistry and Physics. CRC Press.	No abstract available						●				書籍		D	-
31	分析	Jurado-Sánchez, B.; Ballesteros, E.; Gallego, M.	Analytical method for biomonitoring of perfluoroalkyl acids in human urine	2014	Talanta. 2014 Oct;128:141-6. doi: 10.1016	Perfluoroalkyl acids are an important class of synthetic compounds widely used in commercial and residential settings, which may have potential adverse health effects. The objective of this study was to monitor 6 perfluorocarboxylic acids and perfluorooctane sulphonate in human urine to obtain a way to asses exposure. The target analytes were extracted from urine by using a semi automated solid-phase extraction module and derivatised with isobutyl chloroformate by catalysis with 0.03 N,N-dicyclohexylcarbodiimide in pyridine. Determination and quantisation were achieved by gas chromatography with a mass spectrometer detector operating in the selected-ion monitoring mode. The developed approach is fast and provided low limits of detection (0.2-1.0 ng L(-1)) with good precision (relative standard deviation lower than 7.5%, within-day and between day). Recoveries from urine samples, which were spiked with the studied compounds at levels of 10 and 50 ng L(-1) ranged from 0.93 to 96%. Perfluorohexanoic (≤ 70 ng L(-1)) and perfluoroheptanoic acids (<2 ng L(-1)) were found in the urine samples from exposed researchers taken after handling these compounds. From the calculation of the excretion kinetics it was found that the dosage absorbed was eliminated within 15 h after exposure.	●	●		●						-		B	-
32	分析	Jahnke, Annika; Berger, Urs	Trace analysis of per- and polyfluorinated alkyl substances in various matrices— How do current methods perform	2009	J Chromatogr A. 2009 Jan 16;1216(3):410-21. doi: 10.1016/j.chroma.2008.08.098. Epub 2008 Sep 3.	Per- and polyfluorinated alkyl substances (PFAS) are a group of industrial chemicals, some of which have been produced for over 50 years. Scarcely one decade ago, their ubiquity in wildlife, humans and the global environment was discovered. This urged the need for robust and reliable, yet very sensitive analytical methods allowing for their determination in various matrices. This article reviews the state-of-the-art in trace analysis of ionic and neutral PFAS in humans as well as environmental samples such as wildlife, water, solid matrices and air. Analytical protocols for PFAS determination in food and consumer products are also included. The methods are critically discussed in terms of their advantages, shortcomings, possibilities, limitations, and potential for further development.			●		●	●				-		B	-
33	分析	Riddell, Nicole; Arsenault, Gilles; Benskin, Jonathan P; Chittim, Brock; Martin, Jonathan W; McAlees, Alan; McCrindle, Robert	Branched perfluorooctane sulfonate isomer quantification and characterization in blood serum samples by HPLC/ESI-MS(/MS)	2009	Environ Sci Technol. 2009 Oct 15;43(20):7902-8. doi: 10.1021/es901261v.	Perfluorooctane sulfonate (PFOS) is a global contaminant and is currently among the most prominent contaminants in human blood and wildlife samples. Although "total PFOS" (SigmaPFOS) analytical methods continue to be the most commonly used for quantification, recent analytical method developments have made it possible to resolve the various isomers of PFOS by HPLC-MS/MS. Characterized technical PFOS standards (i.e., containing a mixture of PFOS isomers) are now available that enable isomer specific quantification of PFOS, however the advantages of such an analysis have notyet been examined systematically. Herein, PFOS isomers have been individually quantified for the first time in real samples and the results are compared to a traditional SigmaPFOS method; the influence of analytical standards and isomer specific electrospray and MS/ MS behavior were also investigated. The two human serum standard reference materials chosen for analysis contained dramaticallydifferent PFOS isomer profiles (approximately 30-50% total branched isomers) emphasizing that isomer patterns should not be ignored and may provide useful information on exposure sources (i.e., direct exposure to PFOS vs indirect exposure from PFOS-precursors). Depending on the sample and the particular MS/MS transition chosen for SigmaPFOS analysis (i.e., 499-->80 or 499-->99), SigmaPFOS concentrations may be over- or underestimated compared to the isomer specific analysis. Differences in the extent of in-source fragmentation and MS/MS dissociation contributed to the systematic analytical bias. It was also shown that SigmaPFOS data are prone to interlaboratory variation due to various choices of PFOS standards and instrumental conditions used. In the future, for either SigmaPFOS or isomer specific PFOS analyses, we suggest that accuracy can be maximized and interlaboratory discrepancies minimized by using a common chemically pure technical PFOS standard characterized by 19F NMR.			●							-		B	-
34	分析	SamiraSalihovicHelenaNilssonJessikaHagbergGunillaLindström	Trends in the analysis of persistent organic pollutants € (POPs) in human blood	2013	TrAC Trends in Analytical Chemistry. Volume 46, May 2013, Pages 129-138, doi: 10.1016/j.trac.2012.06.009	The general demands on analytical practices in laboratories involved in monitoring concentrations of persistent organic pollutants (POPs) in human blood in the context of the Stockholm Convention are met by the validated analytical procedures applied in most laboratories today. At the same time, as the concentrations of many of the legacy POPs are decreasing in the general populations, more specific, sensitive, and accurate analytical techniques are required. Thus, a challenge for the Stockholm Convention is the analytical capacity, in terms of quality and availability worldwide, to monitor declining concentrations of POPs in human blood. However, other POP issues (e.g., those targeted by epidemiological studies) might require different information and therefore more specialized analytical procedures having greater instrumental sensitivity. We review current and emerging analytical procedures used for analysis of the chlorinated, brominated, and fluorinated classes of POPs in human blood with a focus on the compounds included in the Stockholm Convention. In general, analytical trends in sample clean-up, separation, detection techniques and quality protocols provide a tool for POP laboratories to measure POPs in human blood. Techniques based on established mass-selective instruments are most commonly employed but declining concentrations in humans in the future might require more selective, more sensitive techniques.			●							-		B	-
35	分析	Loewen, Mark; Halldorson, Thor; Wang, Feiyue; Tomy, Gregg	Fluorotelomer carboxylic acids and PFOS in rainwater from an urban center in Canada	2005	Environ Sci Technol. 2005 May 1;39(9):2944-51. doi: 10.1021/es048635b.	A method based on LC/MS/MS analysis of fluorotelomer carboxylic acids (FTCAs: CnF2n+1CH2COOH, n = 6, 8, and 10) and fluorotelomer unsaturated carboxylic acids (FTUCAs: CnF2nCHCOOH, n = 6, 8, and 10) in rainwater using negative ionization electrospray multiple reaction monitoring conditions is described. These compounds are thought to be oxidative products of atmospherically transported fluorotelomer alcohols (FTOHs: CnF2n+1CH2CH2CH2OH). Preconcentration from rainwater samples collected in Winnipeg, Manitoba, Canada, was achieved using solid-phase extraction on C18 sorbent. Low parts per trillion levels of the C10- and C12-FTCAs and FTUCAs were detected, suggesting that one possible pathway of removing FTOHs from the atmosphere is through oxidation and wet deposition. Perfluorocarboxylic acids (PFCAs) and perfluorooctane sulfonate (PFOS) were simultaneously analyzed in the rainwater samples using established LC/MS/MS methods. PFOS was deposited in rainwater with a concentration of 0.59 ng/L while PFCAs were not detected above their respective method detection limits.				●	●	●				-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
36	分析	Reiner, Jessica L; Nakayama, Shoji F; Delinsky, Amy D; Stanko, Jason P; Fenton, Suzanne E; Lindstrom, Andrew B; Strynar, Mark J	Analysis of PFOA in dosed CD1 mice	2009	Reprod Toxicol. 2009 Jun;27(3-4):360-364. doi: 10.1016/j.reprotox.2008.10.006. Epub 2008 Nov 6.	The number of studies involving the analysis of perfluorooctanoic acid (PFOA) has increased recently because PFOA is routinely detected in human blood samples from around the world. Recent studies with mice have shown that dosing pregnant dams with PFOA during gestation gives rise to a dose-dependent mortality in the litters, a reduction in neonatal body weight for the surviving pups, and subsequent deficits in mammary gland development when compared to control animals. The actual body burdens of PFOA in dams and pups associated with these endpoints have not been determined, in part due to a lack of robust analytical methods for these matrices. The goal of the current study was to develop reliable methods with acceptable performance characteristics for the analysis of PFOA in several matrices relevant to pregnant mouse studies. Dam and pup serum, amniotic fluid, urine, milk, mammary tissue, and whole mouse pups were isolated for method development and analysis. The resulting method provided excellent accuracy (92.1-111%) and reproducibility (relative standard deviation 4.3-21%) making them very useful for future studies. These methods were then applied to dosed animal fluids and tissues in order to conduct a thorough evaluation of the pharmacokinetics in utero. Resulting tissue specific measurements of PFOA in serum, amniotic fluid, urine, milk, mammary tissue, and whole pup homogenate will be used to more completely describe the dose-response relationships for the most sensitive health outcomes and inform pharmacokinetic models that are being developed and evaluated.				●						-		B	-
37	分析	So, M K; Taniyasu, S; Lam, P K S; Zheng, G J; Giesy, J P; Yamashita, N	Alkaline digestion and solid phase extraction method for perfluorinated compounds in mussels and oysters from South China and Japan	2006	Arch Environ Contam Toxicol. 2006 Feb;50(2):240-8. doi: 10.1007/s00244-005-7058-x. Epub 2005 Sep 16.	Perfluorinated compounds (PFCs), such as perfluorooctane sulfonate (PFOS), have been identified in the coastal waters of China and Japan. An alkaline digestion method, coupled with solid-phase extraction (SPE), and high-performance liquid chromatography interfaced with high-resolution electrospray tandem mass spectrometry was developed to determine PFCs in mussel and oyster samples from coastal waters of South China and Japan. These techniques produced adequate recoveries and reporting limits with small quantities of PFCs. Concentrations of individual PFCs in mussels and oysters from South China and Japan ranged from 113.6 to 586.0 pg/g, wet weight (ww) for PFOS, 63.1 to 511.6 pg/g, ww for perfluorohexane sulfonate, 9.3 to 30.1 pg/g, ww for perfluorobutane sulfonate and 37.8 to 2957.0 pg/g, ww for perfluorooctane sulfonamide. The quantification of perfluorinated carboxylates was compromised by interferences from carboxylates in the procedural blanks. Perfluoroundecanoate and perfluorononanoate had relatively great blank interferences, which resulted in relatively poor limits of quantification for these compounds. Some PFCs were only identified in a limited number of samples: perfluorododecanoate in samples from Tokyo Bay, Japan (195.9 pg/g, ww); and perfluorodecanoate in Fuzhou, China (131.7 pg/g, ww) and Tokyo Bay (118.6 pg/g, ww). The greatest concentrations of perfluorooctanoate, perfluoroheptanoate, and perfluorohexanoate were observed in samples from Tokyo Bay and Bei Hai, South China.				●						-		B	-
38	分析	Yoo, Hoon; Washington, John W; Jenkins, Thomas M; Ellington, J Jackson	Quantitative determination of perfluorochemicals and fluorotelomer alcohols in plants from biosolid-amended fields using LC/MS/MS and GC/MS	2011	Environ Sci Technol. 2011 Oct 1;45(19):7985-90. doi: 10.1021/es102972m. Epub 2011 Jan 19.	Analytical methods for determining perfluorochemicals (PFCs) and fluorotelomer alcohols (FTOHs) in plants using liquid chromatography/tandem mass spectrometry (LC/MS/MS) and gas chromatography/mass spectrometry (GC/MS) were developed, and applied to quantify a suite of analytes in plants from biosolid-amended fields. Dichloromethane-methanol and ethylacetate were chosen as extracting solutions for PFCs and FTOHs, respectively. Nine perfluorocarboxylic acids (PFCAs), three perfluorosulfonic acids (PFSAs), and ten FTOHs were monitored. Most PFCAs and perfluorooctanesulfonate (PFOS) were quantifiable in plants grown in contaminated soils, whereas PFCs went undetected in plants from two background fields. Perfluorooctanoic acid (PFOA) was a major homologue (~10-200 ng/g dry wt), followed by perfluorodecanoic acid (~3-170 ng/g). [PFOS] in plants (1-20 ng/g) generally was less than or equal to most [PFCAs]. The site-specific grass/soil accumulation factor (GSAF = [PFC](Grass)/[PFC](Soil)) was calculated to assess transfer potentials from soils. Perfluorohexanoic acid had the highest GSAF (= 3.8), but the GSAF decreased considerably with increasing PFCA chain length. Log-transformed GSAF was significantly correlated with the PFCA carbon-length ($p < 0.05$). Of the measured alcohols, 8:2nFTOH was the dominant species (≤1.5 ng/g), but generally was present at ≥10× lower concentrations than PFOA.				●						-		B	-
39	分析	Cochran, RS.	Evaluation of Perfluorinated Compounds in Sediment, Water, and Passive Samplers Collected from the Barksdale Air Force Base	2015	Texas Tech University, [n.l.]. https://ttu-ir.tdl.org/bitstream/handle/2346/63633/COCHRAN-THESIS-2015.pdf?sequence=1&isAllowed=y	Perfluorinated compounds (PFCs) are environmentally persistent surfactants that consist of fully fluorinated carbon chains and a terminal sulfonate or carboxylate polar head moiety. Due to their unique amphiphilic properties, PFCs are used in the manufacturing of products such as aqueous film forming foams (AFFFs). There is cause for concern of PFC contamination near the Barksdale Air Force Base resulting from runoff and ground infiltration of AFFFs that were used during fire training. This study analyzed water and sediment samples that were collected over a 13-month sampling period from bayous upstream and downstream of two fire training areas located on the base to determine the occurrence and magnitude of PFCs. Liquid chromatography coupled with an electrospray ionization-triple stage quadrupole mass spectrometer was used for analysis of 6 different PFCs in sample extractions. Total PFC concentrations in the water and sediment samples ranged from non-detect to 7.1 ng/mL and non-detect to 31.4 ng/g, respectively. Two PFCs of increasing concern, perfluorooctanesulfonic acid and perfluorooctanoic acid, were quantified in 79% and 64% of water samples, respectively. Generally, PFCs containing a sulfonate polar head moiety were quantified more frequently than PFCs containing a carboxylate moiety. The perfluoroalkyl chain length of PFCs also showed significant influence on the PFC concentrations when analyzed using Spearman's rank correlation analysis. A matrix of Spearman's rank correlation coefficients revealed that several water quality parameters (e.g., temperature, dissolved oxygen, ammonium, conductivity) may have a significant relationship with concentration of PFCs in water while parameters such as pH and organic matter content of sediment appeared to have no correlation with PFC concentrations. Concentrations of PFCs detected in water, sediment, and fish samples were then compared to sediment and water column passive sampler data to determine if passive samplers could be used as a less invasive method for estimating PFC concentrations in the environment. The concentrations detected in ediment passive samplers were estimated to be more heavily influenced by the amount of PFCs partitioning to the aqueous phase rather than the amount partitioning to sediment. Perfluorooctanesulfonic acid was the only PFC quantified in 1 water passive sampler. The PFCs that were qualitatively detected in water column passive samplers appeared to be related to PFCs that were detected in fish samples. However, results of both types of passive samplers may be improved by longer deployment in the environment.					●					-		B	-
40	分析	3M Company	Interim report #17-Analysis of Woodbury waste site water samples	2008	Interim report #17-Analysis of Woodbury waste site water samples. Maplewood, Minnesota.	No abstract available					●	●			企業データ		D	-
41	分析	Abe, T; Baba, H; Itoh, E; Tanaka, K	Separation of perfluoroalkylsulfinic acids and perfluoroalkylsulfonic acids by ion-exclusion chromatioography	2001	J Chromatogr A. 2001 Jun 22;920(1-2):173-80. doi: 10.1016/s0021-9673(01)00551-9.	Ion-exclusion chromatography has been successfully applied to the separation of a number of perfluoroalkylsulfinic acids and perfluoroalkylsulfonic acids. The separation of various perfluoroalkylsulfinic and perfluoroalkylsulfonic acids, with different alkyl groups, was investigated on a polymethacrylate-based, weakly acidic, cation-exchange resin (TSK gel OApak-A) in the H+-form and using conductimetric detection. When water was used as the eluent, these perfluoroalkylsulfinic and perfluoroalkylsulfonic acids could not be resolved. When an aqueous solution of benzoic acid and o-phthalic acid was used, the separation of each of these acids occurred. In order to improve their separation, the effect of the addition of methanol and 2,2,2-trifluoroethanol, as organic modifiers, was also investigated.					●	●			-		C	-
42	分析	Arsenault, Gilles; Chittim, Brock; McAlees, Alan; McCrindle, Robert; Riddell, Nicole; Yeo, Brian	Some issue relating to the use of perfluorooctane sulfonate (PFOS) samples as reference standard	2008	Chemosphere. 2008 Jan;70(4):616-25. doi: 10.1016/j.chemosphere.2007.06.087. Epub 2007 Aug 27.	Samples of potassium perfluorooctanesulfonate (PFOSK) from three suppliers were analyzed by LC-ESI-MS/MS for purity and by LC-ESI-MS for the percentage of linear isomer present. Our data indicated that the purity ranged from 80% to 98% and the percentages of linear isomer from 67% to 79%. The proportion of branched isomers present in the samples was also estimated using (19)F NMR. These results agreed quite closely with those found by LC-ESI-MS indicating that there is essentially no difference in overall SIM response factor for the branched isomers vs. that of the linear isomer. Several further observations relevant to the use of standards when analyzing for PFOS were encountered during this study. It appears unlikely that matrix effects attributable to the cation (sodium or potassium) present in PFOSNa or PFOSK internal standards is an issue. In seeking potential matrix effects, it was found that the chromatography was improved substantially when the standard was injected as a solution in 80:20 methanol/water rather than 100% methanol. Notably, in concert with the improvement in chromatography, an increase of about 10% in response was observed. In some closely related studies, when (18)O(2) mass-labeled perfluorohexanesulfonate was used as an internal standard, the actual and theoretical concentration ratios matched closely those for related native sulfonates as long as they did not co-elute. However, when they did co-elute, the peak intensities of the native species were enhanced by about 5%, while those of the labeled compound were suppressed by a similar amount. If this effect were not taken into account, the concentration of the native would be inflated by 10%.					●	●			-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ランク①	文献ランク②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
43	分析	Backe, Will J; Day, Thomas C; Field, Jennifer A	Zwitterionic, cationic, and anionic fluorinated chemicals in aqueous film forming foam formulations and groundwater from U	2013	Environ Sci Technol. 2013 May 21;47(10):5226-34. doi: 10.1021/es3034999. Epub 2013 May 1.	A new analytical method was developed to quantify 26 newly-identified and 21 legacy (e.g. perfluoroalkyl carboxylates, perfluoroalkyl sulfonates, and fluorotelomer sulfonates) per and polyfluorinated alkyl substances (PFAS) in groundwater and aqueous film forming foam (AFFF) formulations. Prior to analysis, AFFF formulations were diluted into methanol and PFAS in groundwater were micro liquid-liquid extracted. Methanolic dilutions of AFFF formulations and groundwater extracts were analyzed by large-volume injection (900 µL) high-performance liquid chromatography tandem mass spectrometry. Orthogonal chromatography was performed using cation exchange (silica) and anion exchange (propylamine) guard columns connected in series to a reverse-phase (C18) analytical column. Method detection limits for PFAS in groundwater ranged from 0.71 ng/L to 67 ng/L, and whole-method accuracy ranged from 96% to 106% for analytes for which matched authentic analytical standards were available. For analytes without authentic analytical standards, whole-method accuracy ranged from 78 % to 144 %, and whole-method precision was less than 15 % relative standard deviation for all analytes. A demonstration of the method on groundwater samples from five military bases revealed eight of the 26 newly-identified PFAS present at concentrations up to 6900 ng/L. The newly-identified PFAS represent a minor fraction of the fluorinated chemicals in groundwater relative to legacy PFAS. The profiles of PFAS in groundwater differ from those found in fluorotelomer- and electrofluorination-based AFFF formulations, which potentially indicates environmental transformation of PFAS.					●	●				-		B	-
44	分析	Berger, U.; Kaiser, M. A.; Kärrman, A.; Barber, J. L.; van Leeuwen, S. P.	Recent developments in trace analysis of poly- and perfluoroalkyl substances	2011	Anal Bioanal Chem. 2011 Jun;400(6):1625-35. doi: 10.1007/s00216-011-4823-8. Epub 2011 Mar 12.	Recent developments, improvements, and trends in the ultra-trace determination of per- and polyfluoroalkyl substances (PFASs) in environmental and human samples are highlighted and the remaining challenges and uncertainties are outlined and discussed. Understanding the analytical implications of such things as adsorption of PFASs to surfaces, effects of differing matrices, varying PFAS isomer response factors, potential bias effects of sampling, sample preparation, and analysis is critical to measuring highly fluorinated compounds at trace levels. These intricate analytical issues and the potential consequences of ignoring to deal with them correctly are discussed and documented with examples. Isomer-specific analysis and the development of robust multi-chemical methods are identified as topical trends in method development for an ever-increasing number of PFASs of environmental and human interest. Ultimately, the state-of-the-art of current analytical method accuracy is discussed on the basis of results from interlaboratory comparison studies.					●	●				-		B	-
45	分析	Berger, Urs; Langlois, Ingrid; Oehme, Michael; Kallenborn, Roland	Comparison of three types of mass spectrometer for high-performance liquid chromatography/mass spectrometry analysis of perfluoroalkylated substances and fluorotelomer alcohol	2004	Eur J Mass Spectrom (Chichester). 2004;10(5):579-88. doi: 10.1255/ejms.679.	The performance of three different types of mass spectrometers (MS) coupled to high performance liquid chromatography (HPLC) was compared for trace analysis of perfluoroalkylated substances (PFAS) and fluorotelomer alcohols (FTOHs). Ion trap MS in the full scan and product ion MS2 mode, time-of-flight (TOF) high resolution MS and quadrupole MS in the selected ion mode as well as triple quadrupole tandem MS were tested. Electrospray ionisation in the negative ion mode [ESI-] was best suited for all instruments and compounds. PFAS could only be separated by a buffered mobile phase, but the presence of buffer suppressed the ionisation of FTOHs. Therefore, two independent chromatographic methods were developed for the two compound classes. Mass spectra and product ion spectra obtained by in-source and collision induced dissociation fragmentation are discussed including ion adduct formation. Product ion yields of PFAS were only in the range of 0.3 to 12%, independent from the applied MS instrument. Ion trap MS2 gave product ion yields of 20 to 62% for FTOHs, whereas only 4.1 to 5.8% were obtained by triple quadrupole tandem MS. Ion trap MS was best suited for qualitative analysis and structure elucidation of branched isomeric structures of PFAS. Providing typical detection limits of 5 ng injected in MS2 mode, it was not sensitive enough for selective trace amount quantification. TOF high resolution MS was the only technique combining high selectivity and excellent sensitivity for PFAS analysis (detection limits of 2 to 10 pg), but lacked the possibility of MS-MS. Triple quadrupole tandem MS was the method of choice for quantification of FTOHs with detection limits in the low pg range. It is also well suited for the determination of PFAS, though its detection limits of 10 to 100 pg in tandem MS mode are about one order of magnitude higher than for TOF MS.					●	●				-		B	-
46	分析	Berryman, D., Salhi, C., Bolduc, A., Deblois , C. and Tremblay, H.	Les composés perfluorés dans les cours d'eau et l'eau potable du Québec méridional	2012	Québec, Ministère du Développement durable, de l' Environnement, de la Faune et des Parcs, Direction du suivi de l'état de l'environnement.	Les composés perfluorés sont des produits chimiques utilisés notamment comme enduits imperméabilisants et antitaches sur une grande gamme de biens de consommation courants : papiers et cartons d'emballage d' aliments, intérieur des boîtes de conserve, tissus, vêtements, tapis, meubles, etc. Certains de ces composés sont très persistants dans l'environnement, bioaccumulables et ont des effets toxiques. C'est pourquoi une rè glementation fédérale, adoptée en 2008, interdit désormais au Canada la fabrication, l'utilisation, la vente et l'importation du PFOS et des produits manufacturés qui en contiennent. De plus, des restrictions visant le PFOA sont en préparation. Ce rapport présente les résultats de deux suivis de composés perfluorés réalisés de 2007 à 2009 dans 10 cours d'eau du Québec méridional, dont le fleuve Saint-Laurent. En tout, 19 sites ont été échantillonnés, dont sept stations d'eau potable, où des prélèvements ont été faits mensuellement à l'eau brute et à l'eau traitée durant un an. Au total, 84 échantillons d'eau potable traitée et 172 échantillons d'eau de surface ou d'eau brute de station d'eau potable ont été analysés. Les résultats démontrent que les composés perfluorés sont présents en quantités mesurables dans les cours d'eau du Québec. Le PFOA, le PFOS, le PFNA et le PFUDA ont été détectés dans respectivement 68, 46, 33 et 10 % des échantillons, alors que le PFHxS, le FHUEA, le FOUEA, le PFOSA et le N-Et PFOSA n'ont été détectés qu'à l'occasion. À la majorité des sites d'échantillonnage, les concentrations mesurées pour chacun des composés varient d'inférieures aux limites de détection à 10 ng/l. Dans le bassin de la rivière Yamaska, des concentrations entre 30 et 100 ng/l ont été mesurées. Il est difficile d'évaluer si les composés perfluorés sont dommageables pour l'environnement à ces concentrations, car pour ces substances, il n'existe pas encore de critères de qualité de l'eau visant la protection de l' environnement. Chose certaine, les concentrations mesurées au Québec ne sont pas plus élevées que celles constatées ailleurs dans le monde. Les concentrations mesurées à l'eau potable traitée, tant pour le PFOA que pour le PFOS, sont de loin inférieures aux critères provisoires pour la qualité de l'eau potable établis par l'Environmental Protection Agency (EPA) des États-Unis. Au Québec comme ailleurs, les stations d'eau potable ne sont pas en mesure de retenir ou de détruire les composés perfluorés. Ainsi, à une station de traitement donnée, les concentrations de ces produits dans l'eau brute et l'eau traitée sont essentiellement les mêmes. Les agglomérations urbaines de Montréal et de Trois-Rivières sont peut-être des sources de composés perfluorés pour le fleuve Saint-Laurent, car les concentrations mesurées à leur aval semblent légèrement plus élevées qu'en amont, quoique les différences observées ne soient pas statistiquement significatives. Par ailleurs, les concentrations de PFOS mesurées en 2009 dans la région de Montréal et à son aval sont légèrement moins élev ées qu'en 2007. Cette diminution est peut-être attribuable à la réglementation fédérale sur cette substance adoptée en 2008. D'autres échantillonnages, sur une plus longue période, seraient nécessaires pour confirmer s'il y a véritablement une tendance à la baisse des concentrations de composés perfluorés dans les cours d'eau du Québec.					●	●				-		B	-
47	分析	Furdui, Vasile I; Crozier, Patrick W; Reiner, Eric J; Mabury, Scott A	Trace level determination of perfluorinated compounds in water by direct injection	2008	Chemosphere. 2008 Aug;73(1 Suppl):S24-30. doi: 10.1016/j.chemosphere.2007.07.085. Epub 2008 May 23.	A new, fast LC-MS/MS method for the determination of perfluorinated surfactants in water samples by direct injection without pre-concentration is reported. The current method requires only 4 min to analyze nine perfluoroalkyl compounds in a single analytical run. Standard addition and internal standard quantification were used to determine the level of some perfluorinated carboxylic and sulfonic acids, including perfluorooctanoic sulfonate (PFOS) and perfluorooctanoic acid (PFOA), in Great Lakes water samples. Statistically significant differences were observed between the results obtained using different quantification methods. A relatively small difference between the PFOS values obtained with the standard addition method, with and without peak area normalization, clearly indicates that standard addition is the best quantification method when mass-labeled standards are not available. Based on the paired t-test statistical analysis, the concentrations calculated using external standardization were the least accurate, with the highest mean difference from the standard addition calculated values. Both PFOS and PFOA were present at less than 10 ng l(-1) in all Great Lake samples. Higher levels were detected in tributaries of Lake Ontario and effluents from sewage treatment plants.					●	●				-		B	-
48	分析	González-Barreiro, C.; Martínez-Carballo, E.; Sitka, A.; Scharf, S.; Gans, O.	Method optimization for determination of selected perfluorinated alkylated substances in water samples	2006	Anal Bioanal Chem. 2006 Dec;386(7-8):2123-32. doi: 10.1007/s00216-006-0902-7.	In recent years perfluorinated alkylated substances (PFAS) have appeared as a new class of global pollutant. Besides being an industrially important group of compounds, PFAS are regarded as highly toxic and extraordinarily persistent chemicals that pervasively contaminate human blood and wildlife throughout the world. They are therefore regarded as PBT (persistent, bioaccumulative, and toxic) chemicals. Two comprehensive methods have been developed for determination of eleven of the most environmentally relevant PFAS (seven perfluoroalkylcarboxylates, two perfluoroalkylsulfonates, and two perfluorooctanesulfonamides) in aqueous samples. The compounds were isolated by liquid-liquid extraction (LLE) and solid-phase extraction (SPE), and identification and quantification of the target analytes were achieved by liquid chromatography-electrospray ionization-tandem mass spectrometry (LC-ESI-MS-MS). With LLE detection limits ranged from 0.26 to 0.62 ng L(-1) for enrichment of 900-mL water samples; recovery of PFAS with a carbon chain longer than C7 was excellent (80-93%). With SPE, carboxylates with carbon chains <C10 could be extracted efficiently (70-98%) under acidic conditions, and PFOS and PFOSA could be extracted efficiently (81% and 96%, respectively) under basic conditions, resulting in MDLs between 0.25 and 0.64 ng L(-1). The LLE method was applied successfully to Austrian wastewater effluent samples.					●	●				-		B	-
49	分析	Hori, Hisao; Hayakawa, Etsuko; Yamashita, Nobuyoshi; Taniyasu, Sachi; Nakata, Fumiya; Kobayashi, Yoshimi	High performance liquid chromatography with conductimetric detection of perfluorocarboxilic acids and perfluorosulfonates	2004	Chemosphere. 2004 Oct;57(4):273-82. doi: 10.1016/j.chemosphere.2004.05.028.	A rapid and simple method for separating and determining various environmentally harmful perfluorocarboxylic acids and perfluorosulfonates was successfully developed using high- performance liquid chromatography with conductimetric detection, for product and waste management of these compounds at manufacturing and processing sites. Compounds having C(3)-C(8) perfluoroalkyl groups were separated using a Tosoh TSKgel Super-ODS column and a mobile phase consisting of a mixture of methanol and aqueous NaH(2)PO(4) at several mixing ratios. The best detection limits for the compounds ranged from 0.12 to 0.66 mg l(-1) (ppm), and linear calibration graphs were obtained up to 87-109 mg l(-1). The combination of this method with concentration of the sample by solid-phase extraction with cartridges based on styrene-divinylbenzene-copolymer enabled the determination of approximately 50 microg l(-1) (ppb) for compounds with C(4)-C(8) perfluoroalkyl groups. This method was successfully used to monitor the artificial decomposition of the perfluorocarboxylic acid n-C(4)F(9)COOH induced by a photocatalyst.					●	●				-		C	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献クラン①①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
50	分析	ISO	ISO 25101 Water quality – Determination of perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) – Method for unfiltered water samples using solid phase extraction and liquid chromatography with mass spectrometry	2009	International Standardization Organization. 25101:2009	ISO 25101:2009 specifies a method for the determination of the linear isomers of perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) in unfiltered samples of drinking water, ground water and surface water (fresh water and sea water) using high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS). Other isomers may be reported separately as non-linear isomers and qualified as such. The method is applicable to a concentration range of 2,0 ng/l to 10 000 ng/l for PFOS and 10 ng/l to 10 000 ng/l for PFOA. Depending on the matrix, the method may also be applicable to higher concentrations ranging from 100 ng/l to 200 000 ng/l after suitable dilution of the sample or reduction in sample size.					●	●				ISO規格		A	-
51	分析	Barbara S Larsen, Mary A Kaiser	Challenges in perfluorocarboxylic acid	2007	Anal Chem . 2007 Jun 1;79(11):3966-73. doi: 10.1021/ac071918c.	No abstract available					●	●				-		C	-
52	分析	Martin, Jonathan W; Kannan, Kurunthachalam; Berger, Urs; de Voogt, Pim; Field, Jennifer; Franklin, James; Giesy, John P; Harner, Tom; Muir, Derek C G; Scott, Brian; Kaiser, Mary; Järnberg, Ulf; Jones, Kevin C; Mabury, Scott A; Schroeder, Horst; Simcik, Matt; Sottani, Christina; van Bavel, Bert; Kärrman, Anna; Lindström, Gunilla; van Leeuwen, Stefan	Analytical challenges hamper perfluoroalkyl research	2004	Environ Sci Technol. 2004 Jul 1;38(13):248A-255A. doi: 10.1021/es0405528.	No abstract available					●	●				-		C	-
53	分析	Moody, C A; Kwan, W C; Martin, J W; Muir, D C; Mabury, S A	Determination of perfluorinated surfactants in surface water samples by two independent analytical techniques: liquid chromatography/ tandem mass spectrometry and 19F NMR	2001	Anal Chem. 2001 May 15;73(10):2200-6. doi: 10.1021/ac0100648.	Perfluorinated surfactants are an important class of specialty chemicals that have received recent attention as a result of their persistence in the environment. Two analytical methods for the determination of perfluorinated surfactants in aqueous samples were developed in order to investigate a spill of 22000 L of fire retardant foam containing perfluorinated surfactants into Etobicoke Creek (Toronto, Ontario). With the first method, aliquots of surface water (0.2-200 mL) were preconcentrated using solid-phase extraction. Liquid chromatography/tandem mass spectrometry was employed for identification and quantification of each perfluorinated surfactant. Total perfluorinated surfactant concentrations in surface water samples ranged from 0.011 to 2270 microg/L, and perfluorooctanesulfonate was the predominant surfactant observed. Interestingly, perfluorooctanoate was detected in surface water sampled upstream of the spill. A second method employing 19F NMR was developed for the determination of total perfluorinated surfactant concentrations in aqueous samples (2-100 mL). By 19F NMR, the surface water concentrations ranged from nondetect (method detection limit, 10 microg/L for a 100-mL sample) to 17000 microg/L. These methods permit comprehensive evaluation of aqueous samples for the presence of perfluorinated surfactants and have applicability to other sample matrixes.					●	●				-		B	-
54	分析	Shoemaker, Jody A; Boutin, Brenda; Grimmett, Paul	Development of a U. S. EPA drinking water method for the analysis of selected perfluoroalkyl acids by solid-phase extraction and LC–MS–MS	2009	J Chromatogr Sci. 2009 Jan;47(1):3-11. doi: 10.1093/chromsci/47.1.3.	A drinking water method for perfluoroalkyl acids (PFAAs) is presented that addresses the occurrence monitoring needs of the U.S. Environmental Protection Agency (EPA) for a future unregulated contaminant monitoring regulation (UCMR). This paper describes the challenges associated with developing an analytical method for 14 PFAAs that will be used for drinking water occurrence monitoring. The method employs solid-phase extraction with analysis by liquid chromatography-tandem mass spectrometry (LC-MS-MS). The final method preservation scheme requires that samples be stored in polypropylene bottles and that they be buffered and free chlorine removed with Trizma buffer. Mean recoveries of chlorinated surface water samples fortified with the PFAAs at 40-100 ng/L (except for the perfluorooctane-sulfonamido-acetic acids at 200 ng/L) are 85-112% with < 5% relative standard deviation. Single laboratory minimum reporting limits of 2.9-14 ng/L are demonstrated with this methodology. The final method meets all of the EPA UCMR survey requirements for sample collection and storage, precision, accuracy, and sensitivity and is expected to be proposed for use under a future UCMR.					●	●				-		B	-
55	分析	Sun, Hongwen; Li, Fasong; Zhang, Tao; Zhang, Xianzhong; He, Na; Song, Qi; Zhao, Lijie; Sun, Lina; Sun, Tieheng	Perfluorinated compounds in surface waters and WWTPs in Shenyang, China: Mass flows and source analysis	2011	Water Res. 2011 Oct 1;45(15):4483-90. doi: 10.1016/j.watres.2011.05.036. Epub 2011 Jun 7.	Concentrations of 10 perfluorinated chemicals (PFCs) were investigated in the Hun River (HR), four canals, ten lakes, and influents and effluents from four main municipal wastewater treatment plants (WWTPs) in Shenyang, China. Mass flows of four main PFCs were calculated to elucidate the contribution from different sections of the HR. Overall, perfluorooctanoic acid (PFOA) and perfluorohexanoic acid (PFHxA) were the major PFCs in the HR, with ranges of 2.68-9.13 ng/L, and 2.12-11.3 ng/L, respectively, while perfluorooctane sulfonate (PFOS) was detected at lower levels, ranging from 0.40 to 3.32 ng/L. The PFC concentrations in the HR increased after the river passes through two cities (Shenyang and Fushun), indicating cities are an important contributor for PFCs. Mass flow analysis in the HR revealed that PFC mass flows from Fushun are 1.65-5.50 kg/year for C6-C8 perfluorinated acids (PFCAs) and 1.29 kg/year for PFOS, while Shenyang contributed 2.83-5.18 kg C6-C8 PFCAs/year, and 3.65 kg PFOS/year. The concentrations of PFCs in four urban canals were higher than those in the HR, with the maximum total PFCs of 240 ng/L. PFOA and PFOS showed different trends along these canals, suggesting different sources for the two PFCs. Total PFCs in ten lakes from Shenyang were at low levels, with the greatest concentration (56.2 ng/L) detected in a heavily industrialized area. The PFC levels in WWTP effluents were higher than those in surface waters with concentrations ranging from 18.4 to 41.1 ng/L for PFOA, and 1.69-3.85 ng/L for PFOS. Similar PFC profiles between effluents from WWTPs and urban surface waters were found. These results indicate that WWTPs are an important PFC source in surface water. Finally, we found that the composition profiles of PFCs in surface waters were similar to those in tap water, but not consistent with those in adult blood from Shenyang. The calculation on total daily intake of PFOS by adults from Shenyang showed that the contribution of drinking water to human exposure was minor.					●	●				-		B	-
56	分析	Szostek, Bogdan; Prickett, Keith B; Buck, Robert C	Determination of fluorotelomer alcohol by liquid chromatography/tandem mass spectrometry in water	2006	Rapid Commun Mass Spectrom. 2006;20(19):2837-44. doi: 10.1002/rcm.2667.	Fluorotelomer alcohols (FTOHs) are important polyfluorinated raw materials that belong to the general category of perfluoroalkyl substances (PFAS). PFAS, including perfluoroalkyl carboxylates (PFCAs) and perfluoroalkyl sulfonates, have recently attracted considerable attention because they are persistent and found globally in the environment. FTOHs are precursors that may degrade in the environment to PFCAs. The development of analytical methods for determination FTOHs in environmental samples is necessary to determine the environmental presence of FTOHs. This work presents the development and validation of a liquid chromatography/tandem mass spectrometry (LC/MS/MS) method for the determination of FTOHs (6-2, 8-2, 10-2) in aqueous samples. Chromatographic conditions were optimized in order to obtain focused FTOH chromatographic peaks. The mobile phase and mass spectrometric conditions were optimized to enable formation of deprotonated FTOH molecules in the negative ion electrospray mode. Two extraction methods were investigated using acetonitrile and methyl tert-butyl ether (MTBE). These methods were validated for a range of environmental water samples fortified with FTOHs at three different levels. Both extraction methods resulted in recoveries from 70 to 120%. Detection limits of FTOHs were estimated to be approximately 0.09 ng/mL for LC/MS/MS detection. An LC/MS method was also developed for FTOH determination with an estimated 1.2 ng/mL limit of detection. Various sample storage scenarios were investigated. It was determined that the aqueous samples of FTOHs are best preserved by storing them frozen in sealed vials with aluminum foil lined septa.					●	●				-		C	-
57	分析	Taniyasu, Sachi; Kannan, Kurunthachalam; So, Man Ka; Gulkowska, Anna; Sinclair, Ewan; Okazawa, Tsuyoshi; Yamashita, Nobuyoshi	Analysis of fluorotelomer alcohols, fluorotelomer acids, and short- and long-chain perfluorinated acids in water and biota	2005	J Chromatogr A. 2005 Nov 4;1093(1-2):89-97. doi: 10.1016/j.chroma.2005.07.053. Epub 2005 Aug 15.	Fluorotelomer alcohols and fluorotelomer acids have been proposed as a source of the perfluorinated carboxylic acids found in remote marine locations. To examine the sources and fate of perfluorinated acids in the environment, a method to determine a wide range of poly- and perfluorinated acids in environmental and biological matrices is needed. In this study, a method has been developed to measure a suite of neutral and acidic fluorochemicals including, fluorotelomer alcohols, fluorotelomer acids, and short- and long-chain perfluorinated acids, in water and biological samples. The method involves solid-phase extraction with weak anion exchange (WAX) cartridges, followed by sequential elution with sodium acetate buffer, methanol, and 0.1% NH4OH in methanol. For biological samples, prior to solid-phase extraction, tissues are digested in 0.5N potassium hydroxide/methanol, diluted in water, and passed through the WAX cartridge. Neutral compounds and telomer alcohols are separated from other poly- and perfluorinated acids. The method is robust (i.e., capable of measuring neutral and acidic compounds), and can be applied for the analysis of a range of poly- and perfluorinated acids, including telomer alcohols, telomer acids, perfluoroalkylcarboxylates, and perfluoroalkylsulfonates in water and biota. With the use of high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS), a method detection limit in the range of several tens to hundreds of parts-per-quadrillion (pg/L) in water and at a few tens to hundreds of parts-per-trillion (pg/g) levels in biological matrices can be achieved.					●	●				-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報抽出対象	文献ランク①	文献ランク②
58	分析	Taniyasu, Sachi; Kannan, Kurunthachalam; Wu, Qian; Kwok, Karen Y; Yeung, Leo W Y; Lam, Paul K S; Chittim, Brock; Kida, Takafumi; Takasuga, Takumi; Tsuchiya, Yoshiteru; Yamashita, Nobuyoshi	Inter-laboratory trials for analysis of perfluooroocatanesulfonate and perfluorooctanoate in water samples: Performance and recommendations	2013	Anal Chim Acta. 2013 Apr 3;770:111-20. doi: 10.1016/j.aca.2013.01.056. Epub 2013 Feb 8.	The ISO 25101 (International Organization for Standardization, Geneva) describes a new international standard method for the determination of perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) in unfiltered samples of drinking and surface waters. The method is based on the extraction of target analytes by solid phase extraction, solvent elution, and determination by high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS). For the determination of the performance of this method, more than 20 laboratories from 9 different countries participated in an inter-laboratory trial in 2006. In addition, inter-laboratory trials were conducted in 2008 and 2009 for the analysis of perfluoroalkylsubstances (PFASs), including PFOS and PFOA, in water samples by following the protocols of Japanese Industrial Standard (JIS). Overall, the repeatability coefficients of variation (i.e., within-laboratory precision) for PFOS and PFOA in all water samples were between 3 and 11%, showing a adequate precision of the ISO and JIS methods. The reproducibility coefficients of variation (i.e., between-laboratory precision) were found to vary within a range of 7-31% for surface water and 20-40% for wastewater. The recoveries of PFOS and PFOA, as a measure of accuracy, varied from 84 to 100% for surface water and from 84 to 100% for wastewater among the samples with acceptable criteria for internal standards recovery. The determined concentrations of PFASs in samples compared well with the "true" values. The results of the inter-laboratory trial confirmed that the analytical methods are robust and reliable and can be used as a standard method for the analysis of target compounds in water samples.					●	●				-		B	-
59	分析	U.S. EPA	EPA Method 537, Determination of selected perfluorinated alkyl acids in drinking water by solid phase extraction and liquid chromatography/tandem mass spectrometry (LC/MS/MS)	2009	EPA Document #: EPA/600/R-08/092	No abstract available					●	●				EPA試験法		B	-
60	分析	U.S. EPA	Provisional health advisories for perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS)	2009	1–5. US EPA Office of Water. https://19january2021snapshot.epa.gov/sites/static/files/2015-09/documents/pfoa-pfos-provisional.pdf	EPA recently concluded limited testing of agricultural sites in Alabama where sewage sludge was applied from a local wastewater treatment plant that receives wastewater from numerous industrial sources, including facilities that manufacture and use perfluorooctanoic acid (PFOA) and other perfluorinated chemicals (PFCs). The results from this limited testing indicated elevated levels of PFCs in the sludge and the soil that received the sludge. As a result, EPA has conducted sampling of public drinking water. The levels of PFOA and perfluorooctane sulfonate (PFOS) recently analyzed in community water systems in Lawrence and Morgan Counties are all lower than 0.04 ppb. Based on its current understanding, EPA believes these levels are not of concern and residents may rely upon public water systems. EPA will soon begin groundwater and surface water sampling to determine if PFOA or PFOS has migrated into any private drinking water supplies and ponds in the affected area. The Office of Water (OW) has developed Provisional Health Advisory values1 for PFOA and PFOS to assess potential risk from exposure to these chemicals through drinking water. Other PFCs have been found at this site. However, information on the toxicity of PFCs other than PFOS and PFOA is limited and therefore no attempt is made at the present time to develop Provisional Health Advisory values for these other PFCs.					●					-		B	-
61	分析	U.S. EPA	The toxicity of perfluoroactanoic acid (PFOA) and of percfluorooctanate sulfonate (PFOS)	2009	Memorandum. Office of Solid Waste and Emergency Response.	No abstract available					●					評価書		D	-
62	分析	U.S. EPA	UCMR3 laboratory approval requirements and information document	2012	Technical support center. Standards and Risk Management Division. Office of Groundwater and Drinking Water. U.S. Environmental Protection Agency, Cincinnati, Ohio 45268.	No abstract available					●					EPAガイダンス		D	-
63	分析	Japanese Industrial Standard	Testing methods for perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) in industrial water and wastewater	2011	Japanese Industrial Standard (2011). JIS K 0450-70-10	(序文) この規格は，2009年に第1版として発行されたISO 25101を基とし，工業用水及び工場排水試験に適応するように，技術的内容を変更して作成した日本工業規格である。 なお，この規格で側線又は点線の下線を施してある箇所は，対応国際規格を変更している事項である。変更の一覧表にその説明を付けて，附属書JDに示す。また，附属書JA～附属書JCは対応国際規格にはない事項である。						●				JIS規格		A	-
64	分析	van Leeuwen, S P J; de Boer, J	Extraction and clean-up strategies for the analysis of poly-and perfluoroalkyl substances in environmental and human matrices	2007	J Chromatogr A. 2007 Jun 15;1153(1-2):172-85. doi: 10.1016/j.chroma.2007.02.069. Epub 2007 Feb 24.	The rapidly expanding field of per- and polyfluorinated alkyl substances (PFASs) research has resulted in a wide range of analytical methodologies to determine the human and environmental exposure to PFASs. This paper reviews the currently applied techniques for sample pre-treatment, extraction and clean-up for the analysis of ionic and non-ionic PFASs in human and environmental matrices. Solid phase extraction (SPE) is the method of choice for liquid samples (e.g. water, blood, serum, plasma), and may be automated in an on-line set-up for (large volume) sample enrichment and sample clean-up. Prior to SPE, sample pre-treatment (filtration or centrifugation for water or protein precipitation for blood) may be required. Liquid-liquid extraction can also be used for liquid samples (and does not require above mentioned sample pretreatment). Solid-liquid extraction is the commonly applied method for solid matrices (biota, sludge, soil, sediment), but automation options are limited due to contamination from polytetrafluorethylene tubings and parts applied in extraction equipment. Air is generally preconcentrated on XAD-resins sandwiched between polyurethane foam plugs. Clean-up of crude extracts is essential for destruction and removal of lipids and other co-extractives that may interfere in the instrumental determination. SPE, (fluorous) silica column chromatography, dispersive graphitized carbon and destructive methods such as sulphuric acid or KOH treatment can be applied for clean-up of extracts. Care should be taken to avoid contamination (e.g. from sample bottles, filters, equipment) and losses of PFASs (e.g. adsorption, volatilization) during sampling, extraction and clean-up. Storage at -20 degrees C is generally appropriate for conservation of samples.						●				-		B	-
65	分析	van Leeuwen, Stefan P J; Karrman, Anna; van Bavel, Bert; de Boer, Jacob; Lindstrom, Gunilla	Struggle of quality in determination of perfluorinated contaminants in environmental and human samples	2006	Environ Sci Technol. 2006 Dec 15;40(24):7854-60. doi: 10.1021/es061052c.	The first worldwide interlaboratory study on the analyses of 13 perfluorinated compounds (PFCs) in three environmental and two human samples indicates a varying degree of accuracy in relation to the matrix or analyte determined. The ability of 38 participating laboratories from 13 countries to determine the analytes in the various matrices was evaluated by calculation of z-scores according to the Cofino model. The PFCs which were reported most frequently by the laboratories, and assessed with the most satisfactory agreement, were perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA). In general, the level of agreement between the participating laboratories decreased in the following order: PFC standard solution (76% satisfactory z-scores of <[2]1 for PFOS) < human blood (67%) < human plasma (63%) < fish liver extract (55%) < water (31%) < fish tissue (17%). This shows that relative good agreement between laboratories was obtained for the study of standard and human matrices. For the fish extract, most laboratories underestimated the actual PFOS concentration due to matrix effects. The results for the fish tissue and water are also poor, indicating that the extraction and cleanup steps require further improvement. It was concluded that the PFC determinations in various matrices are not yet fully mastered.						●			●	-		B	-
66	分析	van Leeuwen, S P J; Swart, C P; van der Veen, I; de Boer, J	Significant improvements in the analysis of perfluorinated compounds in water and fish: Results from an interlaboratory method evaluation study	2009	J Chromatogr A. 2009 Jan 16;1216(3):401-9. doi: 10.1016/j.chroma.2008.11.029. Epub 2008 Nov 18.	The 2nd international interlaboratory study (ILS) on perfluorinated compounds (PFCs) in environmental samples was organized to assess the performance of 21 North American and European laboratories on the analysis of PFCs in water and fish. A study protocol was provided to assess accuracy, precision, matrix effects and to study the use of in-house standards. The participants used shared native and mass-labelled standards that were provided for this study to quantify the PFC concentrations in the samples. Matrix effects in the determination of PFCs can be considerable and can decrease the sensitivity, the accuracy and internal standard recoveries. Therefore, two quantification methods were evaluated by all laboratories: standard addition quantification (SAQ) and solvent-based calibration curve quantification (SBCCQ; using mass-labelled internal standards (IS)). The between laboratory reproducibility (i.e. coefficient of variance) was smaller for the SBCCQ results (except for PFBS and PFHxS for which no mass-labelled analogues were available) compared to those obtained by the SAQ method. The within laboratory precision of individual laboratories is good (mean for all PFCs in water 12% and 6.8% in fish). The good performance is partially attributable to the use of well-defined native- and mass-labelled standards. Therefore, the SBCCQ method is recommended. The results show that analytical methods for PFCs in water and fish have improved considerably. Critical steps identified in this study are (i) the use of well-defined native standards for quantification, (ii) the use of mass-labelled internal standards (preferably one for each target compound) and (iii) minimization of matrix effects by a better clean up.						●				-		B	-
67	分析	Villagrasa, Marta; López de Alda, Maria; Barceló, Damià	Environmental analysis of fluorinated alkyl substances by liquid chromatography-(tandem) mass spectrometry: a review	2006	Anal Bioanal Chem. 2006 Oct;386(4):953-72. doi: 10.1007/s00216-006-0471-9. Epub 2006 May 19.	Fluorinated alkyl substances (FASs) are widely distributed contaminants that have been found in many environmental, human and biological samples throughout the world. Perfluorochemicals are used in many industry and consumer products, such as polymers and surfactants, because they have unique and useful properties (they are stable, chemically inert and generally unreactive). However, these compounds have also been found to be toxic, persistent and bioaccumulative. In recent years various analytical methods have been developed for the analysis of FASs in environmental samples. Most of these methods are based on liquid chromatography coupled to mass spectrometry (LC-MS) or tandem mass spectrometry (LC-MS/MS), since this is considered to be the technique of choice. This article reviews the various LC-(tandem)MS methods described so far for the analysis of FASs in water, sediment, sludge and biota samples. It discusses the main experimental conditions used for sample pretreatment and for analysis as well as the most relevant problems encountered and the limits of detection achieved.						●				-		B	-
68	分析	Villaverde-de-Sﾃ｡a, Eugenia; Fernﾃ｡ndez-Lﾃｳpez, Marﾃｭa; Rodil, Rosario; Quintana, Josﾃｩ Benito; Racamonde, Inﾃｩs; Cela, Rafael	Solid phase extraction of perfluoroalkylated compounds from sea water	2015	J Sep Sci. 2015 Jun;38(11):1942-50. doi: 10.1002/jssc.201401453. Epub 2015 Apr 27.	This study describes an in-depth investigation of the parameters involved in the solid-phase extraction performance of perfluoroalkylated compounds (seven carboxylates and one sulfonate), particularly with sea water samples. The two most popular sorbents, Oasis WAX and Oasis HLB, were considered and it was observed that the high ionic strength of sea water may impair solid-phase extraction recoveries. In the final protocol, Oasis HLB cartridges were selected, incorporating a 10% methanol clean-up step before elution with methanol, since less matrix effects were obtained. The proposed method allows successful recoveries, higher than 71%, and relative standard deviations lower than 20%. It also provides excellent limits of detection values between 0.01 and 0.21 ng/L. Finally, the method was applied to fresh and sea water samples, where several perfluoroalkylated compounds were found at concentrations ranging between 0.16 and 64 ng/L. In the case of perfluorooctane sulfonate, recently included in the Water Frame Directive, its concentration reached the highest values among the perfluoroalkylated compounds measured (64 ng/L in river samples).						●				-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
69	分析	Weremiuk AM, Gerstmann S, Frank H.	Quantitative determination of perfluorinated surfactants in water by LC-MS/MS	2006	J Sep Sci. 2006 Sep;29(14):2251-5. doi: 10.1002/jssc.200600041.	The surfactants perfluorooctanoate (PFOA), perfluorooctane sulfonate (PFOS), and derivatives of the latter have emerged as globally distributed persistent environmental contaminants. Methods for their reliable quantitative determination at ppt-levels (ng/L) are needed in order to detect their main sources, to elucidate their environmental fate, and to identify potential sinks. The common method for water analysis involves preconcentration by SPE followed by LC coupled to ESI MS/MS (LC-ESI-MS/ MS). All sample preparation steps must be carefully optimized in order to arrive at reliable quantitative data. Two major aspects are important: (i) during SPE, contaminations may arise from materials containing traces of PFOA/S; (ii) during LC-ESI-MS/ MS, ionization yields are suppressed by matrix components and depend upon the analyte concentrations in the extracts. The levels of PFOA/S in the river Roter Main near Bayreuth have been determined using the optimized method.						●					-		B	-
70	分析	Susan T. Wolfa and William K. Reagenb	Method for the determination of perfluotrinated compounds (PFCs) in water by solid-phase extraction and liquid chromatography/tandem mass spectrometry (LC/MS/MS	2011	Analytical methods, Issue 7, 2011, doi: 10.1039/C1AY05190C	A solid phase extraction-liquid chromatography tandem mass spectrometry (SPE-LC/MS/MS) analytical method for the analysis of perfluorinated compounds (PFCs) in water is presented. The method incorporates a stable isotope internal standard (IS) for each target analyte added prior to sample collection. Method validation for perfluorinated carboxylic acids (PFCAs) (C4–C12), perfluorinated sulfonic acids (PFSAs) (C4, C6, and C8), and perfluorooctane sulfonamide (PFOSA) in laboratory Milli Q water evaluated the following: (1) method accuracy and precision over the concentration range 0.025 ng mL − 1 to 25 ng mL − 1; (2) internal standard calibration; (3) quantitation of mixed branched and linear isomers of perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) with linear isomer calibration; (4) method minimum reporting levels (MRLs) (Shoemaker et al, http://www.epa.gov/nerlcwww/Method%20537_FINAL_rev1.1.pdf, and Winslow et al, Environ. Sci. Technol., 2006, 40, 281–288); and (5) 28 day holding time at the MRL, low, and mid range of the calibration range. IS calibration with IS addition to the sample bottle prior to sample collection demonstrated an overall method accuracy of at least 100 ± 10% with a precision of ±15% and a 28-day sample holding time at the MRLs for all target analytes. Method application to groundwater, production facility non-contact cooling water, and production facility wastewater treatment effluent samples demonstrated a method accuracy of at least 100 ± 19% with a precision of ±25% for all target analytes.						●					-		B	-
71	分析	Yamashita, Nobuyoshi; Kannan, Kurunthachalam; Taniyasu, Sachi; Horii, Yuichi; Okazawa, Tsuyoshi; Petrick, Gert; Gamo, Toshitaka	Analysis of perflulorinated acids at parts per quadrillion levels in seawater using liquid chromatograph tandem mass spectrometry	2004	Environ Sci Technol. 2004 Nov 1;38(21):5522-8. doi: 10.1021/es0492541.	Perfluorinated acids (PFAs) and their salts have emerged as an important class of global environmental contaminants. Determination of sub-parts-per-trillion or parts-per-quadrillion concentrations of perfluorinated acids in aqueous media has been impeded by relatively high background levels arising from procedural or instrumental blanks. To understand the role of the oceans in the transport and fate of perfluorinated acids, methods to determine ultratrace levels of these compounds in seawater are needed. In this study, sources of procedural and instrumental blank contamination by perfluorinated acids have been identified and eliminated, to reduce background levels in blanks and thereby improve limits of quantitation. The method developed in this study is capable of detecting perfluorooctanesulfonate (PFOS), perfluorohexanesulfonate (PFHS), perfluorobutanesulfonate (PFBS), perfluorooctanoate (PFOA), perfluorononanoate (PFNA), and perfluorooctanesulfonamide (PFOSA) at low pg/L levels in oceanic waters. PFOA is the major perfluorinated compound detected in oceanic waters, followed by PFOS. Further studies are being conducted to elucidate the distribution and fate of perfluorinated acids in oceans.						●			●		-		B	-
72	分析	Khairunnisa Zainuddin; Mohamad Pauzi Zakaria; Ahmed Najat; Najat Al-Odaini	Perfluorooctanoic acid (PFOA) and perfluorooctan sulfonate (PFOS) in surface water from the Langat river, Peninsular Malaysia	2012	Environmental Forensics. 13(1), DOI:10.1080/15275922.2011.643335	This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae, and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand, or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.						●					-		B	-
73	分析	U.S. EPA	Method 537.1 Determination of Selected Per- and Polyflourinated Alkyl Substances in Drinking Water by Solid Phase Extraction and Liquid Chromatography/Tandem Mass Spectrometry (LC/MS/MS)	2009	EPA Document #: EPA/600/R-08/092	No abstract available									●	EPA試験法		A	-
74	ばく露	Eriksson, Ulrika; Kärrman, Anna	World-wide indoor exposure to poly € fluoroalkyl phosphate esters (PAPs) and other PFASs in household dust	2015	Environ Sci Technol. 2015 Dec 15;49(24):14503-11. doi: 10.1021/acs.est.5b00679. Epub 2015 Jun 2.	Human exposure to perfluorooctanoic acid (PFOA) and other per- and polyfluoroalkyl substances (PFASs) is ongoing and in some cases increasing, despite efforts made to reduce emissions. The role of precursor compounds such as polyfluorinated phosphate esters (PAPs) has received increasing attention, but there are knowledge gaps regarding their occurrence and impact on human exposure. In this study, mono-, di-, and triPAPs, perfluorinated alkyl acids (PFAAs), saturated, and unsaturated fluorotelomer carboxylic acids (FTCA/FTUCAs), perfluoroalkane sulfonamides, and sulfonamidethanols (FOSA/FOSEs), and one fluorotelomer sulfonic acid (FTSA)) were compared in household dust samples from Canada, the Faroe Islands, Sweden, Greece, Spain, Nepal, Japan, and Australia. Mono-, di-, and triPAPs, including several diPAP homologues, were frequently detected in dust from all countries, revealing an ubiquitous spread in private households from diverse geographic areas, with significant differences between countries. The median levels of monoPAPs and diPAPs ranged from 3.7 ng/g to 1 023 ng/g and 3.6 ng/g to 692 ng/g, respectively, with the lowest levels found in Nepal and the highest in Japan. The levels of PAPs exceeded those of the other PFAS classes. These findings reveal the importance of PAPs as a source of PFAS exposure worldwide.			●							-		B	-
75	ばく露	Eschauzier, Christian; Raat, Klaasjan J; Stuyfzand, Pieter J; De Voogt, Pim	Perfluorinated alkylated acids in groundwater and drinking water: identification, origin and mobility	2013	Sci Total Environ. 2013 Aug 1;458-460:477-85. doi: 10.1016/j.scitotenv.2013.04.066. Epub 2013 May 18.	Human exposure to perfluorinated alkylated acids (PFAA) occurs primarily via the dietary intake and drinking water can contribute significantly to the overall PFAA intake. Drinking water is produced from surface water and groundwater. Waste water treatment plants have been identified as the main source for PFAA in surface waters and corresponding drinking water. However, even though groundwater is an important source for drinking water production, PFAA sources remain largely uncertain. In this paper, we identified different direct and indirect sources of PFAA to groundwater within the catchment area of a public supply well field (PSWF) in The Netherlands. Direct sources were landfill leachate and water draining from a nearby military base/urban area. Indirect sources were infiltrated rainwater. Maximum concentrations encountered in groundwater within the landfill leachate plume were 1.8 μg/L of non branched perfluorooctanoic acid (L-PFOA) and 1.2 μg/L of perfluorobutanoic acid (PFBA). Sum concentrations amounted to 4.4 μg/L total PFAA. The maximum concentration of ΣPFAA in the groundwater originating from the military camp was around 17 ng/L. Maximum concentrations measured in the groundwater halfway the landfill and the PWSF (15 years travel distance) were 29 and 160 ng/L for L-PFOA and PFBA, respectively. Concentrations in the groundwater pumping wells (travel distance >25 years) were much lower: 0.96 and 3.5 ng/L for L-PFOA and PFBA, respectively. The chemical signature of these pumping wells corresponded to the signature encountered in other wells sampled which were fed by water that had not been in contact with potential contaminant sources, suggesting a widespread diffuse contamination from atmospheric deposition.			●							-		B	-
76	ばく露	Fasano, W J; Kennedy, G L; Szostek, B; Farrar, D G; Ward, R J; Haroun, L; Hinderliter, P M	Penetration of ammonium perfluorooctanoate through rat and human skin in vitro	2005	Drug Chem Toxicol. 2005;28(1):79-90. doi: 10.1081/dct-39707.	Rat and human epidermal membranes were mounted onto in vitro diffusion cells with an exposure area of 0.64 cm2, and skin integrity was confirmed using electrical impedance. Following membrane selection, Fluorad FC-118, a 20% aqueous solution of ammonium perfluorooctanoate (AFPO), was applied to the epidermal surface of each skin replicate at approximately 150 microL/cm2 and the donor chamber opening occluded with Parafilm. Serial receptor fluid samples were collected hourly from 1 to 6 h and at 12, 24, 30, and 48 h and analyzed by liquid chromatography-mass spectrometry (LC-MS) for APFO anion (PFO-). For rat skin, the time to steady-state penetration (6500+/-3000 ng APFO x cm(-2) x h(-1)) occurred in less than 12 h, which was sustained until termination (48 h). Based on the concentration of the applied test material, the permeability coefficient (Kp) for APFO in rat skin was calculated to be 3.25+/-1.51 x 10(-5) cm/h. By end of the 48-h exposure period, only a small portion of the total APFO applied (1.44+/-1.13%) had penetrated through rat skin. For human skin, steady-state penetration of APFO (190+/-57 ng APFO x cm(-2) x h(-1)) was reached by 12 h. Based on the concentration of the applied test material, the permeability coefficient for APFO in human skin was calculated to be 9.49+/-2.86 x 10(-7) cm/h. By the end of the 48-h exposure period, only a negligible amount of the total APFO applied (0.048+/-0.01%) had penetrated through human skin. Thus, under infinite dose and occlusive conditions, the steady-state penetration of APFO from a 20% solution was approximately 34-fold faster through rat skin than human skin.		●	●	●	●	●				-		B	-
77	ばく露	Saito, Norimitsu; Harada, Kouji; Inoue, Kayoko; Sasaki, Kazuaki; Yoshinaga, Takeo; Koizumi, Akio	Perfluorooctanoate and perfluorooctanesulfonate concentrations in surface water in Japan	2004	J Occup Health. 2004 Jan;46(1):49-59. doi: 10.1539/joh.46.49.	Perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) are synthetic surfactants used in Japan. An epidemiological study of workers exposed to PFOA revealed a significant increase in prostate cancer mortality. A cross-sectional study of PFOA-exposed workers showed that PFOA perturbs sex hormone homeostasis. We analyzed their concentrations in surface water samples collected from all over Japan by LC/MS with a solid phase extraction method. The lowest limits of detection (LOD) (ng/L) were 0.06 for PFOA and 0.04 for PFOS. The lowest limits of quantification (LOQ) (ng/L) were 0.1 for both analytes. The levels [geometric mean (GM); geometric standard deviation (GS)] (ng/L) of PFOA and PFOS in the surface waters were GM (GS): 0.97 (3.06) and 1.19 (2.44) for Hokkaido-Tohoku (n=16); 2.84(3.56) and 3.69 (3.93) for Kanto (n=14); 2.50 (2.23) and 1.07 (2.36) for Chubu (n=17); 21.5 (2.28) and 5.73 (3.61) for Kinki (n=8); 1.51 (2.28) and 1.00 (3.42) for Chugoku (n=9); 1.93 (2.40) and 0.89 (3.09) for Kyushu-Shikoku (n=15). The GM of PFOA in Kinki was significantly higher than in other areas (ANOVA p<0.01). Systematic searches of Yodo and Kanzaki Rivers revealed two highly contaminated sites, a public-water-disposal site for PFOA and an airport for PFOS. The former was estimated to release 18 kg of PFOA/d. PFOA in drinking water in Osaka city [40 (1.07) ng/L] was significantly higher than in other areas. The present study confirms that recognizable amounts of PFOA are released in the Osaka area and that people are exposed to PFOA through drinking water ingestion.			●							-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献ランク①	文献ランク②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
78	ばく露	Taniyasu, Sachi; Senthilkumar, Kurunthachalam; Yamazaki, Eriko; Yeung, Leo W Y; Guruge, Keerthi S; Kannan, Kurunthachalam; Yamashita, Nobuyoshi	Perfluoroalkyl substances in the blood of wild rats and mice from 47 prefectures in Japan: use of samples from nationwide specimen bank	2013	Arch Environ Contam Toxicol. 2013 Jul;65(1):149-70. doi: 10.1007/s00244-013-9878-4. Epub 2013 Mar 14.	Numerous studies have reported on the global distribution, persistence, fate, and toxicity of perfluoroalkyl and polyfluoroalkyl substances (PFASs). However, studies on PFASs in terrestrial mammals are scarce. Rats can be good sentinels of human exposure to toxicants because of their habitat, which is in close proximity to humans. Furthermore, exposure data measured for rats can be directly applied for risk assessment because many toxicological studies use rodent models. In this study, a nationwide survey of PFASs in the blood of wild rats as well as surface water samples collected from rats' habitats from 47 prefectures in Japan was conducted. In addition to known PFASs, combustion ion chromatography technique was used for analysis of total fluorine concentrations in the blood of rats. In total, 216 blood samples representing three species of wild rats (house rat, Norway rats, and field mice) were analyzed for 23 PFASs. Perfluorooctanesulfonate (PFOS; concentration range <0.05-148 ng/mL), perfluorooctane sulfonamide (PFOSA; <0.1-157), perfluorododecanoate (<0.05-5.8), perfluoroundecanoate (PFUnDA; <0.05-51), perfluorodecanoate (PFDA; <0.05-9.7), perfluorononanoate (PFNA; <0.05-249), and perfluorooctanoate (PFOA) (<0.05-60) were detected >80 % of the blood samples. Concentrations of several PFASs in rat blood were similar to those reported for humans. PFSAs (mainly PFOS) accounted for 45 % of total PFASs, whereas perfluoroalkyl carboxylates (PFCAs), especially PFUnDA and PFNA, accounted for 20 and 10 % of total PFASs, respectively. In water samples, PFCAs were the predominant compounds with PFOA and PFNA found in >90 % of the samples. There were strong correlations ($p < 0.001$ to $p < 0.05$) between human population density and levels of PFOS, PFNA, PFOA, and PFOSA in wild rat blood.			●							-	1	A	-
79	ばく露	Harada, K; Nakanishi, S; Saito, N; Tsutsui, T; Koizumi, A	Airborne perfluorooctanoate may be a substantial source contamination in Kyoto area, Japan	2005	Bull Environ Contam Toxicol. 2005 Jan;74(1):64-9. doi: 10.1007/s00128-004-0548-0.	No abstract available				●						アブストなし、要確認？		D	-
80	ばく露	Kaboré, Hermann A; Vo Duy, Sung; Munoz, Gabriel; Méité, Ladji; Desrosiers, Mélanie; Liu, Jinxia; Sory, Traoré Karim; Sauvé, Sébastien	Worldwide drinking water occurrence and levels of newly-identified perfluoroalkyl and polyfluoroalkyl substances	2018	Sci Total Environ. 2018 Mar;616-617:1089-1100. doi: 10.1016/j.scitotenv.2017.10.210.	In the last decade or so, concerns have arisen with respect to the widespread occurrence of perfluoroalkyl acids (PFAAs) in the environment, food, drinking water, and humans. In this study, the occurrence and levels of a large range of perfluoroalkyl and polyfluoroalkyl substances (PFASs) were investigated in drinking water (bottled and tap water samples) from various locations around the world. Automated off-line solid phase extraction followed by ultra-high-performance liquid chromatography coupled to high-resolution mass spectrometry was used to analyze PFASs of various chain lengths and functional groups. In total, 29 target and 104 suspect-target PFASs were screened in drinking water samples (n=97) from Canada and other countries (Burkina Faso, Chile, Ivory Coast, France, Japan, Mexico, Norway, and the USA) in 2015-2016. Out of the 29 PFASs quantitatively analyzed, perfluorocarboxylates (PFCAs: C(4/14)), perfluoroalkane sulfonates (PFSAs: C(4), C(6), C(8)), and perfluoroalkyl acid precursors (e.g., 5:3 fluorotelomer carboxylate (5:3 FTCA)) were recurrently detected in drinking water samples (concentration range: <LOD to 39ngL(-1)). Tap water samples from Canada showed noteworthy differences depending on their source; for instance, Σ(29)PFASwas significantly greater in those produced from the Great Lakes/St. Lawrence River ecosystem than those produced from other types of sources (14 versus 5.3ngL(-1), respectively). A suspect-target screening approach indicated that other perfluoroalkane sulfonamides (FBSA, FHxSA), perfluoroethyl cyclohexane sulfonate (PFECHS), ultrashort chain (C(2)-C(3)) PFSAs (PFEtS, PFPrS), and two additional PFSAs (PFPeS (C(5)) and PFHpS (C(7))) were repeatedly present in tap water samples (concentration ranges: <LOD to 4.0ngL(-1)). To the authors' best knowledge, this constitutes the first observation of a cyclic perfluoroalkane sulfonate (PFECHS) and C(4)-C(6) perfluoroalkane sulfonamides (FBSA, FHxSA) in drinking water. According to the newly updated US EPA health advisory for PFOS and PFOA (70ngL(-1)), the drinking water samples collected in the present monitoring would not pose a health risk to consumers as regards PFAA levels.				●					●	-		B	-
81	ばく露	Mak, Yim Ling; Taniyasu, Sachi; Yeung, Leo W Y; Lu, Guohui; Jin, Ling; Yang, Yongliang; Lam, Paul K S; Kannan, Kurunthachalam; Yamashita, Nobuyoshi	Perfluorinated compounds in tap water from China and several other countries	2009	Environ Sci Technol. 2009 Jul 1;43(13):4824-9. doi: 10.1021/es900637a.	The recent development of a sensitive and accurate analytical method for the analysis of 20 perfluorinated compounds (PFCs), including several short-chain PFCs, has enabled their quantification in tap water collected in China, Japan, India, the United States, and Canada between 2006 and 2008. Of the PFCs measured, PFOS, PFHxS, PFBS, PFPrS, PFEtS, PFOSA, N-EtFOSAA, PFDoDA, PFUnDA, PFDA, PFNA, PFHpA, PFHxA, PFPeA, PFBA, and PFPrA were found at detectable concentrations in the tap water samples. The water samples from Shanghai (China) contained the greatest concentrations of total PFCs (arithmetic mean = 130 ng/L), whereas those from Toyama (Japan) contained only 0.62 ng/L. In addition to PFOS and PFOA, short-chain PFCs such as PFHxS, PFBS, PFHxA, and PFBA were found to be prevalent in drinking water. According to the health-based values (HBVs) and advisory guidelines derived for PFOS, PFOA, PFBA, PFHxS, PFBS, PFHxA, and PFPeA by the U.S.EPA and the Minnesota Department of Health, tap water may not pose an immediate health risk to consumers.				●	●	●				-		B	-
82	ばく露	Moriwaki, Hiroshi; Takatah, Yumiko; Arakawa, Ryuichi	Concentrations of perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) in vacuum cleaner dust collected in Japanese homes	2003	J Environ Monit. 2003 Oct;5(5):753-7. doi: 10.1039/b307147m.	Perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) are shown to be globally distributed, environmentally persistent and bioaccumulative. Although there is evidence that these compounds exist in the serum of non-occupationally exposed humans, the pathways leading to the presence of PFOS and PFOA are not well characterized. The concentrations of PFOS and PFOA in the vacuum cleaner dust collected in Japanese homes were measured. The compounds were detected in all the dust samples and the ranges were 11-2500 ng g(-1) for PFOS and 69-3700 ng g(-1) for PFOA. It was ascertained that PFOS and PFOA were present in the dust in homes, and that the absorption of the dust could be one of the exposure pathways of the PFOS and PFOA to humans. With regard to risk management, it is important to consider the usage of PFOS and PFOA in the indoor environment in order to avoid further pollution.				●						-		B	-
83	ばく露	Harada, K; Saito, N; Sasaki, K; Inoue, K; Koizumi, A	Perfluoroocatne sulfonate contamination of drinking water in the Tama river, Japan: Estimated effects on resident serum levels	2003	Bull Environ Contam Toxicol. 2003 Jul;71(1):31-6. doi: 10.1007/s00128-003-0126-x.	No abstract available					●	●				-		B	-
84	ばく露	Yukioka, Satoru; Tanaka, Shuhei; Suzuki, Yuji; Echigo, Shinya; Kärrman, Anna; Fujii, Shigeo	A profile analysis with suspect screening of per- and polyfluoroalkyl substances (PFASs) in firefighting foam impacted waters in Okinawa, Japan	2020	Water Res. 2020 Oct 1;184:116207. doi: 10.1016/j.watres.2020.116207. Epub 2020 Jul 20.	Per- and polyfluoroalkyl substances (PFASs) are a group of persistent contaminants detected in firefighting foam impacted waters. Previous studies have performed suspect and non-target screening by high-resolution mass spectrometry (HRMS) to determine the composition of PFAS contamination and to discover unknown PFASs. Here, we performed a profile analysis with suspect screening against two lists in the NORMAN Suspect List Exchange in firefighting foam impacted environmental and drinking water (n = 18) collected in Okinawa, Japan, in April 2019. Samples were analyzed by liquid chromatography (LC) quadrupole time-of-flight (QTOF) MS in electron spray ionization mode. Suspect screening returned 116 candidate PFASs with their molecular weights, functional groups, and perfluoroalkyl chain lengths. Long-chain perfluoroalkyl acids (PFAAs) and some of their precursors were specifically found around the firefighting training area. Short-chain PFAAs were assumed to be formed from precursors by environmental processes. Perfluoroalkyl sulfonamide precursors were found to be transformed to perfluoroalkyl sulfonic acids (PFSAs) in the drinking water treatment process. In contrast, biological activated carbon filtration formed perfluoroalkyl carboxylic acids (PFCAs). The PFAS profile showed that a large number of different substances needs to be considered.									●	-	1	A	-
85	バイオモニタリング	Abdallah, M. A.; Wemken, N.; Drage, D. S.; Tlustos, C.; Cellarius, C.; Cleere, K.; Morrison, J. J.; Daly, S.; Coggins, M. A.; Harrad, S.	Concentrations of perfluoroalkyl substances in human milk from Ireland: Implications for adult and nursing infant exposure	2019	Chemosphere. 2020 May;246:125724. doi: 10.1016/j.chemosphere.2019.125724.	Concentrations of 10 perfluoroalkyl substances (PFASs) were measured in 16 pools of human milk from Ireland. Only four PFASs were detected (PFOA, PFNA, PFHxS and PFOS), with concentrations dominated by PFOA which was detected in all samples at a median of 0.10 ng/mL. Concentrations and the relative abundance of PFASs in human milk from Ireland are within the range reported for other countries. Estimated exposures for nursing infants to perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) do not suggest a health concern. A one compartment pharmacokinetic model was used to predict the intakes of PFOS and PFOA required to support the observed concentrations in human milk. This suggests current adult exposure in Ireland to PFOS is below the provisional tolerable weekly intake (TWI) proposed by EFSA. In contrast, the model predicts that the maximum concentration detected in human milk in this study, implies a level of adult exposure that would exceed EFSA's provisional TWI for PFOA. As exposure of the Irish population to PFASs via drinking water, indoor air and dust is well-characterised, current understanding suggests that the major contributor to overall exposure of the Irish population is via the diet and/or less well-studied pathways like dermal uptake from PFAS-containing fabrics and cosmetics.	●	●								-		B	-
86	バイオモニタリング	Apelberg, B. J.; Goldman, L. R.; Calafat, A. M.; Herbstman, J. B.; Kuklenyik, Z.; Heidler, J.; Needham, L. L.; Halden, R. U.; Witter, F. R.	Determinants of fetal exposure to polyfluoroalkyl compounds in Baltimore, Maryland	2007	Environ Sci Technol. 2007 Jun 1;41(11):3891-7. doi: 10.1021/es0700911.	Polyfluoroalkyl compounds (PFCs), such as perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA), are ubiquitous, man-made chemicals. Human data suggest that in utero exposures to these chemicals occur and some evidence of developmental toxicity in animals exists. To assess the distribution and determinants of fetal exposure to PFCs, we analyzed cord serum samples from 299 singleton newborns delivered between 2004 and 2005 in Baltimore, MD for 10 PFCs by employing on-line solid-phase extraction coupled with reversed-phase high-performance liquid chromatography-tandem mass spectrometry. PFOS and PFOA were detected in 99 and 1 of umbilical cord sera, with geometric mean concentrations of 4.9 and 1.6 ng/mL, respectively. PFOS and PFOA concentrations were highly correlated (Pearson's $r = 0.64$ after natural log transformation, $p < 0.01$). Eight other PFCs were detected less frequently and at lower concentrations than PFOS and PFOA. Geometric mean concentrations of PFOS for Asians (6.0 ng/mL) and Blacks (5.1 ng/mL) were higher than those for Whites (4.2 ng/mL), while PFOA levels were more evenly distributed by race. Other maternal demographic and socioeconomic characteristics, including age, education, marital status, and living in the city limits were not significantly associated with cord concentrations. Our findings suggest that in utero exposure to PFOS and PFOA is ubiquitous in a population of babies born in Baltimore, MD.	●	●	●	●						-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
87	バイオモニタリング	Brede, E.; Wilhelm, M.; Göen, T.; Müller, J.; Rauchfuss, K.; Kraft, M.; Hölzer, J.	Two-year follow-up biomonitoring pilot study of residents' and controls' PFC plasma levels after PFOA reduction in public water system in Arnsberg, Germany	2010	Int J Hyg Environ Health. 2010 Jun;213(3):217-23. doi: 10.1016/j.ijheh.2010.03.007. Epub 2010 May 21.	Residents in Arnsberg, Germany, had been supplied by drinking water contaminated with perfluorooctanoate (PFOA). Biomonitoring data from 2006 evidenced that plasma PFOA concentrations of residents from Arnsberg were 4.5-8.3 times higher than those in reference groups. The introduction of charcoal filtration in July 2006 distinctly reduced PFOA concentrations in drinking water. Our one-year follow-up study showed a 10-20% reduction of PFOA plasma levels in residents from Arnsberg. Here we report the first results of the two-year follow-up study Arnsberg 2008 Additionally, the results of the two-year follow-up examination of the reference group are included. Paired plasma samples of 138 study participants (45 children, 46 mothers and 47 men) collected in 2006 and 2008 were considered in the statistical analyses. Within the two years plasma concentrations of PFOA, perfluorooctanesulfonate (PFOS) and perfluorohexanesulfonate (PFHxS) decreased in residents from Arnsberg and in control groups. The geometric means of PFOA plasma levels declined by 0.39 (children and mothers) and 0.26 (men) in Arnsberg and by 13-15% in the corresponding subgroups from the reference areas. For the population from Arnsberg a geometric mean plasma PFOA half-life of 3.26 years (range 1.03-14.67 years) was calculated. Our results confirm an ongoing reduction of the PFOA load in residents from Arnsberg. The decline of PFC levels in plasma of participants from the reference areas reflects the general decrease of human PFC exposure during the very recent years.	●	●			●			●	-		B	-
88	バイオモニタリング	Calafat, A. M.; Kato, K.; Hubbard, K.; Jia, T.; Botelho, J. C.; Wong, L. Y.	Legacy and alternative per- and polyfluoroalkyl substances in the U	2019	Environ Int. 2019 Oct;131:105048. doi: 10.1016/j.envint.2019.105048. Epub 2019 Jul 31.	Concerns are heightened from detecting environmentally persistent man-made per- and polyfluoroalkyl substances (PFAS) in drinking water systems around the world. Many PFAS, including perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA), remain in the human body for years. Since 1999-2000, assessment of exposure to PFOS, PFOA, and other select PFAS in the U.S. general population has relied on measuring PFAS serum concentrations in participants of the National Health and Nutrition Examination Survey (NHANES). Manufacturers have replaced select chemistries ("legacy" PFAS) with PFAS with shorter biological half-lives (e.g., GenX, perfluorobutanoate [PFBA]) which may efficiently eliminate in urine. However, knowledge regarding exposure to these compounds is limited. We analyzed 2682 urine samples for 17 legacy and alternative PFAS in 2013-2014 NHANES participants ≥6 years of age. Concentrations of some of these PFAS, measured previously in paired serum samples from the same NHANES participants, suggested universal exposure to PFOS and PFOA, and infrequent or no exposure to two short-chain PFAS, perfluorobutane sulfonate and perfluoroheptanoate. Yet, in urine, PFAS were seldom detected; the frequency of not having detectable concentrations of any of the 17 PFAS was 67.5%. Only two were detected in >1.5% of the population: PFBA -0.133 and perfluorohexanoate (PFHxA, 22.6%); the 90th percentile urine concentrations were 0.1 μg/L (PFBA), and 0.3 μg/L (PFHxA). These results suggest that exposures to short-chain PFAS are infrequent or at levels below those that would result in detectable concentrations in urine. As such, these findings do not support biomonitoring of short-chain PFAS or fluorinated alternatives in the general population using urine, and highlight the importance of selecting the adequate biomonitoring matrix.	●	●							-		B	-
89	バイオモニタリング	De Felip, E.; Abballe, A.; Albano, F. L.; Battista, T.; Carraro, V.; Conversano, M.; Franchini, S.; Giambanco, L.; Iacovella, N.; Ingelido, A. M.; Maiorana, A.; Maneschi, F.; Marra, V.; Mercurio, A.; Nale, R.; Nucci, B.; Panella, V.; Pirola, F.; Porpora, M. G.; Procopio, E.; Suma, N.; Valentini, S.; Valsenti, L.; Vecchiè, V.	Current exposure of Italian women of reproductive age to PFOS and PFOA: A human biomonitoring study	2015	Chemosphere. 2015 Oct;137:1-8. doi: 10.1016/j.chemosphere	Perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) concentrations were determined in serum samples collected in 2011-2012 from 549 nulliparous Italian women of reproductive age who resided in six different Italian Regions. Assessment of exposure to perfluorinated compounds was part of a large human biomonitoring study (Project Life Plus "Womenbiopop") that aimed at examining the exposure of women of reproductive age to priority organic pollutants. The median concentrations of PFOS and PFOA were 2.43, and 1.55ngg(-1), respectively. Significant differences in the concentrations of both compounds were observed among the six Regions. Women from central Italy had the highest levels of both compounds, followed by women from northern Italy, and southern Italy. No differences in the PFOS concentrations were found between women from urban/industrial areas and women from rural areas, whereas the levels of PFOA were significantly higher in women residing in urban/industrial areas than in women residing in rural areas. Taken together, the observed concentrations confirm that the overall exposure of the Italian population is among the lowest observed in industrialized countries. A downward temporal trend in exposure was observed for both compounds when comparing the results from the present study with those assessed in a study conducted in 2008	●	●							-		B	-
90	バイオモニタリング	Jain, R. B.; Ducatman, A.	Roles of gender and obesity in defining correlations between perfluoroalkyl substances and lipid/lipoproteins	2019	Sci Total Environ. 2019 Feb 25;653:74-81. doi: 10.1016/j.scitotenv.2018.10.362. Epub 2018 Oct 29.	Data from National Health and Nutrition Examination Survey (NHANES) for 2005-2014 for those aged ≥20 years fasting for ≥8 h (N = 3629) were analyzed to evaluate the role that gender and obesity play in defining correlations between selected perfluoroalkyl substances (PFAS) and total cholesterol (TC), low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), and triglycerides. PFAS considered for analyses were: perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), perfluorodecanoic acid (PFDA), perfluorononanoic acid (PFNA), perfluorohexane sulfonate (PFHxS), perfluoroundecanoic acid (PFUnDA), and 2-(N-methyl-perfluorooctane sulfonamido) acetic acid (Me-FOSAA). Gender and obesity stratified regression models were fitted to estimate associations between PFAS and lipid/lipoproteins with adjustments made for confounders. For obese males, but not for nonobese males, positive associations were found between TC and LDL with PFOA (β = 0.0519, p = 0.01 for TC and β = 0.0822, p = 0.03 for LDL), and PFNA (β = 0.0328, p = 0.03 for TC and β = 0.0679, p = 0.04 for LDL). For obese females, adjusted concentrations of TC increased with increase in the concentrations of PFDA (β = 0.0247, p = 0.048), PFNA (β = 0.0286, p = 0.04), and Me-PFOSAA (β = 0.0274, p = 0.02), and there was a positive association of LDL with PFOS (β = 0.0375, p = 0.04), PFDA (β = 0.0397, p = 0.047), and PFNA (β = 0.0593, p = 0.02). The findings, concerning the relationship of longer chain PFAS to serum lipids, suggest greater susceptibility to elevated TC and LDL cholesterol in the obese participants, with some differences between men and women. The key contributing modifiable risk for nonalcoholic steatosis is obesity, and, the development of nonalcoholic steatosis is recognized to be sexually dimorphic. The epidemiologic observation of a susceptible obese subgroup in our data is consistent with toxicology literature findings of disrupted cholesterol metabolism via induced steatosis following PFAS exposure. Gender differences affect serum concentration of PFAS during the reproductive years, and our data add a secondary question concerning whether they also affect the interaction between PFAS exposure and lipid handling in males and females.	●	●	●						-		B	-
91	バイオモニタリング	Černá, Milena; Grafnetterová, Anna Pinkr; Dvořáková, Darina; Pulkrabová, Jana; Malý, Marek; Janoš, Tomáš; Vodrážková, Nicole; Tupá, Zdeňka; Puklová, Vladimíra	Biomonitoring of PFOA, PFOS and PFNA in human milk from Czech Republic, time	2020	Environ Res. 2020 Sep;188:109763. doi: 10.1016/j.envres.2020.109763. Epub 2020 Jun 3.	BACKGROUND: Perfluoralkylated substances (PFASs) are persistent and bioaccumulative environmental contaminants. They are included on the list of emergent compounds monitored in the frame of HBM4EU project. OBJECTIVES: To analyze PFASs levels in human milk samples collected in the period 2006 through 2017, to follow their time trends, to assess the PFASs exposure in breastfed infants, to calculate the daily intake of PFASs and to compare it with the tolerable daily/weekly) intakes and to quantify risk from exposure using the hazard quotient and hazard index approach. MATERIAL AND METHODS: A broad spectrum of PFASs were analyzed by means of UHPLC-MS/MS in primipara human milk samples collected in four consecutive time periods 2006, 2010/11, 2014, and 2017; N = 46, 183, 164 and 232, respectively. Mothers living in urban and suburban residences were recruited after their delivery at maternity hospitals, and milk samples were taken within 2 and 8 weeks after delivery. The questionnaire was focused on possible sources of exposure, dietary habits and lifestyle. RESULTS: Only perfluorooctane sulfonate (PFOS) and perfluorooctanoid acid PFOA (in 2017, also perfluorononanoic acid (PFNA)) were quantified in more than 90% of analyzed human milk samples. In all sampling periods, the levels of PFOA were higher than those of PFOS (p < 0.05). A significant downward temporal trend (p < 0.001) was observed for both PFOA and PFOS levels. The median concentrations in sampling years 2006, 2010/11, 2014, and 2017 were 0.075, 0.059, 0.035, and 0.023 ng/mL for PFOA and 0.045, 0.031, 0.029, and 0.020 ng/mL for PFOS, respectively. In 2017, PFNA was also quantified in 99% of samples with the median concentration of 0.007 ng/mL. The levels of PFASs correlated with maternal sea fish consumption. No maternal age-related relationship was observed. Using the tolerably daily intake (TDI) values for PFOS and PFOA set by the European Food Safety Authority (EFSA) in 2008, the calculated daily intakes from breastfeeding were clearly below these limits. Using the new, more conservative EFSA Provisional Tolerably Weekly Intake (PTWI) values set in 2018, we demonstrated a considerable exceedance of PTWI, with a hazard index above 1. CONCLUSION: Significant time-related decreasing trends in the PFOS and PFOA levels in human milk were observed. Nevertheless, the body burden of infants from breastfeeding might pose an enhanced health risk to infants when the current PTWI values are applied. These findings strongly support the present EU efforts to phase out PFOA, its salts and PFOA related compounds. Since PFOS exposure there has still been widely detected despite PFOS usage reduction measures, the major exposure routes should be further monitored and, if possible, eliminated.	●							●	-		B	-
92	バイオモニタリング	Shin, Hyeong-Moo; Vieira, Verónica M; Ryan, P Barry; Steenland, Kyle; Bartell, Scott M	Retrospective exposure estimation and predicted versus observed serum perfluorooctanoic acid concentrations for participants in the C8 Health Project	2011	Environ Health Perspect. 2011 Dec;119(12):1760-5. doi: 10.1289/ehp.1103729. Epub 2011 Aug 3.	BACKGROUND: People living or working in eastern Ohio and western West Virginia have been exposed to perfluorooctanoic acid (PFOA) released by DuPont Washington Works facilities. OBJECTIVES: Our objective was to estimate historical PFOA exposures and serum concentrations experienced by 45,276 non-occupationally exposed participants in the C8 Health Project who consented to share their residential histories and a 2005-2006 serum PFOA measurement. METHODS: We estimated annual PFOA exposure rates for each individual based on predicted calibrated water concentrations and predicted air concentrations using an environmental fate and transport model, individual residential histories, and maps of public water supply networks. We coupled individual exposure estimates with a one-compartment absorption, distribution, metabolism, and excretion (ADME) model to estimate time-dependent serum concentrations. RESULTS: For all participants (n = 45,276), predicted and observed median serum concentrations in 2005-2006 are 14.2 and 24.3 ppb, respectively [Spearman's rank correlation coefficient (r(s)) = 0.67]. For participants who provided daily public well water consumption rate and who had the same residence and workplace in one of six municipal water districts for 5 years before the serum sample (n = 1,074), predicted and observed median serum concentrations in 2005-2006 are 32.2 and 40.0 ppb, respectively (r(s) = 0.82). CONCLUSIONS: Serum PFOA concentrations predicted by linked exposure and ADME models correlated well with observed 2005-2006 human serum concentrations for C8 Health Project participants. These individualized retrospective exposure and serum estimates are being used in a variety of epidemiologic studies being conducted in this region.	●	●		●					-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
93	バイオモニタリング	Wong, F.; Macleod, M.; Mueller, J. F.; Cousins, I. T.	Enhanced elimination of perfluorooctane sulfonic acid by menstruating women: evidence from population-based pharmacokinetic modeling	2014	Environ Sci Technol. 2014;48(15):8807-14. doi: 10.1021/es500796y. Epub 2014 Jul 8.	Human biomonitoring studies have shown that concentrations of perfluorooctane sulfonic acid (PFOS) in men are higher than in women. We investigate sex differences in elimination of PFOS by fitting a population-based pharmacokinetic model to six cross-sectional data sets from 1999 to 2012 from the US National Health and Nutrition Examination Survey (NHANES) and derive human first-order elimination rate constants (kE) and corresponding elimination half-lives (t1/2) for PFOS, where t1/2 = ln 2/kE. We use a modified version of the Ritter population-based pharmacokinetic model and derive elimination rate constants separately for men and women. The model accounts for population-average lifetime changes in PFOS intake, body weight, and menstruation rate. We compare the model-derived elimination rate constant for hypothetical nonmenstruating women to the elimination rate constant for men and women when menstruation is included as a loss process to evaluate the hypothesis that loss of PFOS by menstruation is an important process for women. The modeled elimination half-life for men is 4.7 years, and the modeled elimination half-life for women when excluding losses from menstruation is 3.7 years. The elimination half-life for women when menstruation is included in the model is 4 years. Thus, menstruation accounts for 0.3 of the discrepancy in elimination of PFOS between men and women. The remaining discrepancy is likely due to other sex-specific elimination routes that are not considered in our modeling.	●	●	●	●					●	-		B	-
94	バイオモニタリング	Butenhoff, John L; Olsen, Geary W; Pfahles-Hutchens, Andrea	The applicability of biomonitoring data for perfluorooctanesulfonate to the environmental public health continuum	2006	Environ Health Perspect. 2006 Nov;114(11):1776-82. doi: 10.1289/ehp.9060.	Perfluorooctanesulfonate and its salts (PFOS) are derived from perfluorooctanesulfonyl fluoride, the basic chemical building block for many sulfonyl-based fluorochemicals used as surfactants and for their repellent properties. PFOS is highly persistent in the environment and has a long serum elimination half-life in both animals and humans. PFOS has been detected globally in the environment and in blood serum in various populations throughout the world, with the majority of human sampling done in the United States and Japan. The mechanisms and pathways leading to the presence of PFOS in human blood are not well characterized but likely involve both direct exposures to PFOS or chemicals and materials that can degrade to PFOS, either in the environment or from industrial and commercial uses. In 2000 the 3M Company, a major manufacturer, announced a phaseout of PFOS-related materials. Animal studies indicate that PFOS is well absorbed orally and distributes mainly in blood serum and the liver. Several repeat-dose toxicology studies in animals consistently demonstrated that the liver is the primary target organ. In addition there is a steep dose response for mortality in sexually mature rats and primates as well as in neonatal rats and mice exposed in utero. Several biomonitoring research needs that have been identified on PFOS include additional data from general populations pertaining to other matrices besides blood; matched serum and urine samples from humans and research animals; and comparison of whole blood, serum, and plasma concentrations from the same individuals.			●							-		B	-
95	バイオモニタリング	Frisbee, Stephanie J; Brooks, A Paul Jr; Maher, Arthur; Flensborg, Patsy; Arnold, Susan; Fletcher, Tony; Steenland, Kyle; Shankar, Anoop; Knox, Sarah S; Pollard, Cecil; Halverson, Joel A; Vieira, Verónica M; Jin, Chuanfang; Leyden, Kevin M; Ducatman, Alan M	The C8 health project: design, methods, and participants	2009	Environ Health Perspect. 2009 Dec;117(12):1873-82. doi: 10.1289/ehp.0800379. Epub 2009 Jul 13.	BACKGROUND: The C8 Health Project was created, authorized, and funded as part of the settlement agreement reached in the case of Jack W. Leach, et al. v. E.I. du Pont de Nemours & Company (no. 01-C-608 W.Va., Wood County Circuit Court, filed 10 April 2002). The settlement stemmed from the perfluorooctanoic acid (PFOA, or C8) contamination of drinking water in six water districts in two states near the DuPont Washington Works facility near Parkersburg, West Virginia. OBJECTIVES: This study reports on the methods and results from the C8 Health Project, a population study created to gather data that would allow class members to know their own PFOA levels and permit subsequent epidemiologic investigations. METHODS: Final study participation was 69,030, enrolled over a 13-month period in 2005-2006. Extensive data were collected, including demographic data, medical diagnoses (both self-report and medical records review), clinical laboratory testing, and determination of serum concentrations of 10 perfluorocarbons (PFCs). Here we describe the processes used to collect, validate, and store these health data. We also describe survey participants and their serum PFC levels. RESULTS: The population geometric mean for serum PFOA was 32.91 ng/mL, 500% higher than previously reported for a representative American population. Serum concentrations for perfluorohexane sulfonate and perfluorononanoic acid were elevated 39% and 73% respectively, whereas perfluorooctanesulfonate was present at levels similar to those in the U.S. population. CONCLUSIONS: This largest known population study of community PFC exposure permits new evaluations of associations between PFOA, in particular, and a range of health parameters. These will contribute to understanding of the biology of PFC exposure. The C8 Health Project also represents an unprecedented effort to gather basic data on an exposed population; its achievements and limitations can inform future legal settlements for populations exposed to environmental contaminants.			●	●	●	●			●	-		B	-
96	バイオモニタリング	Kato, Kayoko; Wong, Lee-Yang; Jia, Lily T; Kuklenyik, Zsuzsanna; Calafat, Antonia M	Trends in exposure to polyfluoroalkyl chemicals in the U	2011	Environ Sci Technol. 2011 Oct 1;45(19):8037-45. doi: 10.1021/es1043613. Epub 2011 Apr 6.	Since 2002, practices in manufacturing polyfluoroalkyl chemicals (PFCs) in the United States have changed. Previous results from the National Health and Nutrition Examination Survey (NHANES) documented a significant decrease in serum concentrations of some PFCs during 1999-2004. To further assess concentration trends of perfluorooctane sulfonate (PFOS), perfluorooctanoate (PFOA), perfluorohexane sulfonate (PFHxS), and perfluorononanoate (PFNA), we analyzed 7876 serum samples collected from a representative sample of the general U.S. population ≥12 years of age during NHANES 1999-2008. We detected PFOS, PFOA, PFNA, and PFHxS in more than 95% of participants. Concentrations differed by sex regardless of age and we observed some differences by race/ethnicity. Since 1999-2000, PFOS concentrations showed a significant downward trend, because of discontinuing industrial production of PFOS, but PFNA concentrations showed a significant upward trend. PFOA concentrations during 1999-2000 were significantly higher than during any other time period examined, but PFOA concentrations have remained essentially unchanged during 2003-2008. PFHxS concentrations showed a downward trend from 1999 to 2006, but concentrations increased during 2007-2008. Additional research is needed to identify the environmental sources contributing to human exposure to PFCs. Nonetheless, these NHANES data suggest that sociodemographic factors may influence exposure and also provide unique information on temporal trends of exposure.			●	●	●	●				-		B	-
97	バイオモニタリング	Kato, Kayoko; Kalathil, Akil A; Patel, Ayesha M; Ye, Xiaoyun; Calafat, Antonia M	Per- and polyfluoroalkyl substances and fluorinated alternatives in urine and serum by on-line solid phase extraction-liquid chromatography-tandem mass spectrometry	2018	Chemosphere. 2018 Oct;209:338-345. doi: 10.1016/j.chemosphere.2018.06.085. Epub 2018 Jun 14.	Per- and polyfluoroalkyl substances (PFAS), man-made chemicals with variable length carbon chains containing the perfluoroalkyl moiety (C(n)F(2n+1)-), are used in many commercial applications. Since 1999-2000, several long-chain PFAS, including perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA), have been detected at trace levels in the blood of most participants of the National Health and Nutrition Examination Survey (NHANES)-representative samples of the U.S. general population-while short-chain PFAS have not. Lower detection frequencies and concentration ranges may reflect lower exposure to short-chain PFAS than to PFOS or PFOA or that, in humans, short-chain PFAS efficiently eliminate in urine. We developed on-line solid phase extraction-HPLC-isotope dilution-MS/MS methods for the quantification in 50 μL of urine or serum of 15 C(3)-C(11) PFAS (C(3) only in urine), and three fluorinated alternatives used as PFOA or PFOS replacements: GenX (ammonium salt of 2,3,3,3,-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)-propanoate, also known as HFPO-DA), ADONA (ammonium salt of 4,8-dioxa-3H-perfluorononanoate), and 9Cl-PF3ONS (9-chlorohexadecafluoro-3-oxanonane-1-sulfonate), main component of F53-B. Limit of detection for all analytes was 0.1 ng/mL. To validate the method, we analyzed 50 commercial urine/serum paired samples collected in 2016 from U.S. volunteers with no known exposure to the chemicals. In serum, detection frequency and concentration patterns agreed well with those from NHANES. By contrast, except for perfluorobutanoate, we did not detect long-chain or short-chain PFAS in urine. Also, we did not detect fluorinated alternatives in either urine or serum. Together, these results suggest limited exposure to both short-chain PFAS and select fluorinated alternatives in this convenience population.			●							-		B	-
98	バイオモニタリング	Mørck, Thit A; Nielsen, Flemming; Nielsen, Jeanette K S; Siersma, Volkert D; Grandjean, Philippe; Knudsen, Lisbeth E	PFAS concentrations in plasma samples from Danish school children and their mothers	2015	Chemosphere. 2015 Jun;129:203-9. doi: 10.1016/j.chemosphere.2014.07.018. Epub 2014 Aug 18.	Perfluoroalkyl substances (PFASs) are accumulating in our environment and human exposure to these potentially harmful chemicals are of growing concern. In the present study, 116 children aged 6-11 and 143 mothers in two locations in Denmark donated blood samples as a supplement to their participation in the large European human biomonitoring project. DEMOCOPHES (Demonstration of a study to COordinate and Perform Human Biomonitoring on a European Scale). The blood samples were analyzed by LC-MS/MS for the concentration of six PFASs: PFOA, PFHxS, PFNA, PFDA, br-PFOS and n-PFOS. All measured compounds were above the detection limit in both mothers and children except for PFHxS in one child. There was a significant correlation between the levels in children and their mothers, indicating a family-related exposure pattern. However, we also found that the levels of PFOA, PFNA, PFDA, br-PFOS and total-PFOS were significantly higher in children compared to their mothers. This may be due to higher exposure in children through for example dust and soil, and due to the fact that children are smaller in body size and blood volume and hence have a lower storage capacity. Furthermore, we found an association between plasma levels and the age of the mothers and higher levels of plasma PFASs in mothers with low parity. There were no associations between PFAS concentrations and residential area, dietary habits of the participants or with respect to the birth order of the children. The levels are comparable to concentrations found in other Western countries.			●							-		B	-
99	バイオモニタリング	Okada, Emiko; Kashino, Ikuko; Matsuura, Hideyuki; Sasaki, Seiko; Miyashita, Chihiro; Yamamoto, Jun; Ikeno, Tamiko; Ito, Yoichi M; Matsumura, Toru; Tamakoshi, Akiko; Kishi, Reiko	Temporal trends of perfluoroalkyl acids in plasma samples of pregnant women in Hokkaido, Japan, 2003-2011	2013	Environ Int. 2013 Oct;60:89-96. doi: 10.1016/j.envint.2013.07.013. Epub 2013 Sep 6.	Perfluoroalkyl acids (PFAAs) are persistent organic pollutants that are used in a wide range of consumer products. Recent epidemiological studies have shown that prenatal exposure to toxic levels of PFAAs in the environment may adversely affect fetal growth and humoral immune response in infants and children. Here we have characterized levels of prenatal exposure to PFAA between 2003 and 2011 in Hokkaido, Japan, by measuring PFAA concentrations in plasma samples from pregnant women. The study population comprised 150 women who enrolled in a prospective birth cohort study conducted in Hokkaido. Eleven PFAAs were measured in maternal plasma samples using simultaneous analysis by ultra-performance liquid chromatography coupled to triple quadrupole tandem mass spectrometry. At the end of the study, in 2011, age- and parity-adjusted mean concentrations of perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), perfluorododecanoic acid (PFDoDA), perfluorotridecanoic acid (PFTrDA), perfluorohexane sulfonate (PFHxS), and perfluorooctane sulfonate (PFOS) were 1.35ng/mL, 1.26ng/mL, 0.66ng/mL, 1.29ng/mL, 0.25ng/mL, 0.33ng/mL, 0.28ng/mL, and 3.86ng/mL, respectively. Whereas PFOS and PFOA concentrations declined 8.4%/y and 3.1%/y, respectively, PFNA and PFDA levels increased 4.7%/y and 2.4%/y, respectively, between 2003 and 2011. PFUnDA, PFDoDA, and PFTrDA were detected in the vast majority of maternal samples, but no significant temporal trend was apparent. Future studies must involve a larger population of pregnant women and their children to determine the effects of prenatal exposure to PFAA on health outcomes in infants and children.			●							-	1	A	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ラン①	文献ラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
100	バイオモニタリング	Fujii, Yukiko; Yan, Junxia; Harada, Kouji H; Hitomi, Toshiaki; Yang, Hyeran; Wang, Peiyu; Koizumi, Akio	Levels and profiles of long-chain perfluorinated carboxylic acids in human breast milk and infant formulas in East Asia	2012	Chemosphere. 2012 Jan;86(3):315-21. doi: 10.1016/j.chemosphere.2011.10.035. Epub 2011 Nov 21.	In this study, 90 human breast milk samples collected from Japan, Korea, and China were analyzed for perfluorooctanoic acid (PFOA) (C8), perfluorononanoic acid (PFNA) (C9), perfluorodecanoic acid (PFDA) (C10), perfluoroundecanoic acid (PFUnDA) (C11), perfluorododecanoic acid (PFDoDA) (C12), and perfluorotridecanoic acid (PFTrDA) (C13). In addition, infant formulas (n = 9) obtained from retail stores in China and Japan were analyzed. PFOA was the predominant compound and was detected in more than 60% of samples in all three countries. The PFOA, PFNA, PFDA, and PFUnDA levels in Japan were significantly higher than those in Korea and China (p<0.05). The PFTrDA level was highest in Korea (p<0.05). The median PFOA concentrations were 89 pg mL(-1) (48% of total perfluorinated carboxylic acids (PFCAs) (C8-C13)) in Japan, 62 pg mL(-1) (54%) in Korea, and 51 pg mL(-1) (61%) in China. The remaining ∑PFCAs (C9-C13) were 95 pg mL(-1) in Japan, 52 pg mL(-1) in Korea, and 33 pg mL(-1) in China. Among the long-chain PFCAs, odd-numbered PFCAs were more frequently detected than even-numbered PFCAs, except for PFDA in Japan. There were no evident correlations between the mother's demographic factors and the PFCA concentrations. PFOA, PFNA, and PFDA were frequently detected in both Japan and China, but there were no significant differences between the two countries. The total PFCA concentrations in the infant formulas were lower than those in the breast milk samples in Japan (p<0.05), but not in China (p>0.05). In conclusion, various PFCAs were detected in human breast milk samples from East Asian countries.				●						-		1	A	-
101	バイオモニタリング	Hoffman, Kate; Webster, Thomas F; Bartell, Scott M; Weisskopf, Marc G; Fletcher, Tony; Vieira, Verónica M	Private drinking water wells as a source of exposure to perfluorooctanoic acid (PFOA) in communities surrounding a fluoropolymer production facility	2011	Environ Health Perspect. 2011 Jan;119(1):92-7. doi: 10.1289/ehp.1002503. Epub 2010 Oct 4.	BACKGROUND: The C8 Health Project was established in 2005 to collect data on perfluorooctanoic acid (PFOA, or C8) and human health in Ohio and West Virginia communities contaminated by a fluoropolymer production facility. OBJECTIVE: We assessed PFOA exposure via contaminated drinking water in a subset of C8 Health Project participants who drank water from private wells. METHODS: Participants provided demographic information and residential, occupational, and medical histories. Laboratory analyses were conducted to determine serum-PFOA concentrations. PFOA data were collected from 2001 through 2005 from 62 private drinking water wells. We examined the relationship between drinking water and PFOA levels in serum using robust regression methods. As a comparison with regression models, we used a first-order, single-compartment pharmacokinetic model to estimate the serum:drinking-water concentration ratio at steady state. RESULTS: The median serum PFOA concentration in 108 study participants who used private wells was 75.7 μg/L, approximately 20 times greater than the levels in the U.S. general population but similar to those of local residents who drank public water. Each 1 μg/L increase in PFOA levels in drinking water was associated with an increase in serum concentrations of 141.5 μg/L (95% confidence interval, 134.9-148.1). The serum:drinking-water concentration ratio for the steady-state pharmacokinetic model was 114. CONCLUSIONS: PFOA-contaminated drinking water is a significant contributor to PFOA levels in serum in the study population. Regression methods and pharmacokinetic modeling produced similar estimates of the relationship.				●						-			B	-
102	バイオモニタリング	Ye, Xiaoyun; Kato, Kayoko; Wong, Lee-Yang; Jia, Tao; Kalathil, Akil; Latremouille, John; Calafat, Antonia M	Per- and polyfluoroalkyl substances in sera from children 3 to 11 years of age participating in the National Health and Nutrition Examination Survey 2013-2014	2018	Int J Hyg Environ Health. 2018 Jan;221(1):9-16. doi: 10.1016/j.ijheh.2017.09.011. Epub 2017 Sep 29.	Several per- and polyfluoroalkyl substances (PFAS) have been measured in U.S. National Health and Nutrition Examination Survey (NHANES) participants 12 years of age and older since 1999-2000, but PFAS data using NHANES individual samples among children younger than 12 years do not exist. To obtain the first nationally representative PFAS exposure data in U.S. children, we quantified serum concentrations of 14 PFAS including perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorohexane sulfonic acid (PFHxS), and perfluorononanoic acid (PFNA), in a nationally representative subsample of 639 3-11year old participants in NHANES 2013-2014. We used on-line solid-phase extraction coupled to isotope dilution-high performance liquid chromatography-tandem mass spectrometry; limits of detection were 0.1ng/mL for all analytes. We calculated geometric mean concentrations, determined weighted Pearson correlations, and used linear regression to evaluate associations of sex, age (3-5 vs 6-11 years), race/ethnicity (Hispanic vs non-Hispanic), household income, and body mass index with concentrations of PFAS detected in more than 60% of participants. We detected PFOS, PFOA, PFHxS, and PFNA in all children at concentrations similar to those of NHANES 2013-2014 adolescents and adults, suggesting prevalent exposure to these PFAS or their precursors among U.S. 3-11year old children, most of whom were born after the phase out of PFOS in the United States in 2002. PFAS concentration differences by sex, race/ethnicity, and age suggest lifestyle differences that may impact exposure, and highlight the importance of identifying exposure sources and of studying the environmental fate and transport of PFAS.				●						-			B	-
103	バイオモニタリング	Harada, Kouji; Saito, Norimitsu; Inoue, Kayoko; Yoshinaga, Takeo; Watanabe, Takao; Sasaki, Shiro; Kamiyama, Shigetoshi; Koizumi, Akio	The influence of time, sex and geographic factors on levels of perfluorooctane sulfonate and perfluorooctanoate in human serum over the last 25 years	2004	J Occup Health. 2004 Mar;46(2):141-7. doi: 10.1539/joh.46.141.	Perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) are important perfluorochemicals (PFCs) in various applications. Recently, it has been shown that these chemicals are widespread in the environment, wildlife and humans. But the kinds of factors that affect their levels in serum are unclear, and it is also not clear whether exposure to them is increasing or not. To investigate the impacts of time, geographical location and sex on the levels of these chemicals, we measured PFOS and PFOA concentrations in human sera samples collected both historically and recently in Miyagi, Akita and Kyoto Prefectures in Japan. The PFOS and PFOA levels in sera [Geometric Mean (Geometric Standard Deviation)] (microg/L) in 2003 ranged from 3.5 (2.9) in Miyagi to 28.1 (1.5) in Kyoto for PFOS and from 2.8 (1.5) to 12.4 (1.4) for PFOA. Historical samples collected from females demonstrated that PFOS and PFOA concentrations have increased by factors of 3 and 14, respectively, over the past 25 yr. There are large sex differences in PFOS and PFOA concentrations in serum at all locations. Furthermore, there are predominant regional differences for both PFOS and PFOA concentrations. In Kyoto the concentrations of PFOA in dwellers who had lived in the Kinki area for more than 2 yr were significantly higher than in people who had recently moved into the area, in both sexes. This finding suggests that there are sources of PFOA in the Kinki area that have raised the PFOA serum levels of its inhabitants. Further studies are needed to elucidate these sources in the Kinki area of Japan.					●	●				-		1	A	-
104	ADME	3M Company	Determination of serum half-lives of several fluorochemicals, Interim report #1, June 8, 2000 [TSCA Submission]	2000	U.S.EPA AR226-0610.	No abstract available	●	●							企業データ		D	D
105	ADME	Andersen, M. E.; Butenhoff, J. L.; Chang, S. C.; Farrar, D. G.; Kennedy, G. L.; Lau, C.; Olsen, G. W.; Seed, J.; Wallace, K. B.	Perfluoroalkyl acids and related chemistries--toxicokinetics and modes of action	2007	Toxicology. 2006 Oct 3;227(1-2):156-64. doi: 10.1016/j.tox.2006.08.004. Epub 2006 Aug 12.	The perfluoroalkyl acid salts (both carboxylates and sulfonates, hereafter designated as PFAAs) and their derivatives are important chemicals that have numerous consumer and industrial applications. However, recent discoveries that some of these compounds have global distribution, environmental persistence, presence in humans and wildlife, as well as toxicity in laboratory animal models, have generated considerable scientific, regulatory, and public interest on an international scale. The Society of Toxicology Contemporary Concepts in Toxicology Symposium, entitled "Perfluoroalkyl Acids and Related Chemistries: Toxicokinetics and Modes-of-Action Workshop" was held February 14-16, 2007 at the Westin Arlington Gateway, Arlington, VA. In addition to the Society of Toxicology, this symposium was sponsored by 3M Company, DuPont, Plastics Europe, and the U.S. Environmental Protection Agency. The objectives of this 3-day meeting were to -1 provide an overview of PFAA toxicity and description of recent findings with the sulfonates, carboxylates, and telomer alcohols; -2 address the toxicokinetic profiles of various PFAAs among animal models and humans, and the biological processes that are responsible for these observations; -3 examine the possible modes of action that determine the PFAA toxicities observed in animal models, and their relevance to human health risks; and -4 identify the critical research needs and strategies to fill the existing informational gaps that hamper risk assessment of these chemicals. This report summarizes the discourse that occurred during the symposium.	●	●		●						-			C	B
106	ADME	Andersen, M. E.; Clewell, H. J.; Tan, Y. M.; Butenhoff, J. L.; Olsen, G. W.	Pharmacokinetic modeling of saturable, renal resorption of perfluoroalkylacids in monkeys--probing the determinants of long plasma half-lives	2006	Toxicology. 2006 Oct 3;227(1-2):156-64. doi: 10.1016/j.tox.2006.08.004.	Perfluorooctanoate (PFOA) and perfluorooctanesulfonate (PFOS) compounds associated with surface protection product manufactures are distributed globally. The 3-5-year half-lives, reproductive and liver toxicity in animals, and lack of understanding of the factors regulating retention in the body have led to a world-wide public concern for use of these materials. Using a novel physiologically-motivated pharmacokinetic model for renal clearance, perfluoroalkylacid pharmacokinetics in monkeys was successfully described by renal resorption via high efficiency transporters for both intravenous and oral dosing. Intravenous dosing with both PFOA and PFOS in Cynomolgus monkeys produced time course curves consistent with a two-compartment distribution. Extending the PK model for intravenous dosing to examine blood and urine time course data for repeated oral dosing clearly identified the saturable renal resorption. Resorption depends on kinetic factors for transport (T(mC), transport maximum; K(T), transport affinity) and free fraction in plasma (f(plasma)). For PFOA, these parameters were estimated to be 5mg/(h kg) (T(mC)), 0.055 mg/L (K(T)), and 0.02 (f(plasma)). PFOS has longer half-life and had respective values of 13.6 mg/(h kg), 0.023 mg/L, and 0.025. PFOS appeared to have a higher transport capacity and lower affinity than PFOA. Human kinetics indicates even higher resorption efficiency.	●	●		●	●	●	●			-			B	B
107	ADME	Aylward, L. L.; Hays, S. M.; Kirman, C. R.; Marchitti, S. A.; Kenneke, J. F.; English, C.; Mattison, D. R.; Becker, R. A.	Relationships of chemical concentrations in maternal and cord blood: a review of available data [Review]	2014	J Toxicol Environ Health B Crit Rev. 2014;17(3):175-203. doi: 10.1080/10937404.2014.884956.	The developing fetus is likely to be exposed to the same environmental chemicals as the mother during critical periods of growth and development. The degree of maternal-fetal transfer of chemical compounds will be affected by chemical and physical properties such as lipophilicity, protein binding, and active transport mechanisms that influence absorption and distribution in maternal tissues. However, these transfer processes are not fully understood for most environmental chemicals. This review summarizes reported data from more than 100 studies on the ratios of cord:maternal blood concentrations for a range of chemicals including brominated flame-retardant compounds, polychlorinated biphenyls (PCB), polychlorinated dibenzodioxins and dibenzofurans, organochlorine pesticides, perfluorinated compounds, polyaromatic hydrocarbons, metals, and tobacco smoke components. The studies for the chemical classes represented suggest that chemicals frequently detected in maternal blood will also be detectable in cord blood. For most chemical classes, cord blood concentrations were found to be similar to or lower than those in maternal blood, with reported cord:maternal ratios generally between 0.1 and 1 Exceptions were observed for selected brominated flame-retardant compounds, polyaromatic hydrocarbons, and some metals, for which reported ratios were consistently greater than 1 Careful interpretation of the data in a risk assessment context is required because measured concentrations of environmental chemicals in cord blood (and thus the fetus) do not necessarily imply adverse effects or risk. Guidelines and recommendations for future cord:maternal blood biomonitoring studies are discussed.	●	●								-			C	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報抽出対象	文献ランク①	文献ランク②
108	ADME	Beesoon, S.; Martin, J. W.	Isomer-Specific Binding Affinity of Perfluorooctanesulfonate (PFOS) and Perfluorooctanoate (PFOA) to Serum Proteins	2015	Environ Sci Technol. 2015 May 5;49(9):5722-31. doi: 10.1021/es505399w. Epub 2015 Apr 13. . 2015 May 5;49(9):5722-31. doi: 10.1021/es505399w. Epub 2015 Apr 13.	Perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) are among the most prominent contaminants in human serum, and these were historically manufactured as technical mixtures of linear and branched isomers. The isomers display unique pharmacokinetics in humans and in animal models, but molecular mechanisms underlying isomer-specific PFOS and PFOA disposition have not previously been studied. Here, ultrafiltration devices were used to examine (i) the dissociation constants (Kd) of individual PFOS and PFOA isomers with human serum albumin (HSA) and (ii) relative binding affinity of isomers in technical mixtures spiked to whole calf serum and human serum. Measurement of HSA Kd's demonstrated that linear PFOS (Kd = 8(±4) × 10(-8) M) was much more tightly bound than branched PFOS isomers (Kd range from 8(±1) × 10(-5) M to 4(±2) × 10(-4) M). Similarly, linear PFOA (Kd = 1(±0.9) × 10(-4) M) was more strongly bound to HSA compared to branched PFOA isomers (Kd range from 4(±2) × 10(-4) M to 3(±2) × 10(-4) M). The higher binding affinities of linear PFOS and PFOA to total serum protein were confirmed when both calf serum and human serum were spiked with technical mixtures. Overall, these data provide a mechanistic explanation for the longer biological half-life of PFOS in humans, compared to PFOA, and for the higher transplacental transfer efficiencies and renal clearance of branched PFOS and PFOA isomers, compared to the respective linear isomer.		●		●	●	●	●			-	1	A	A
109	ADME	Beesoon, S.; Webster, G. M.; Shoeib, M.; Harner, T.,om; Benskin, J. P.; Martin, J. W.	Isomer Profiles of Perfluorochemicals in Matched Maternal, Cord, and House Dust Samples: Manufacturing Sources and Transplacental Transfer	2011	Environ Health Perspect. 2011 Nov;119(11):1659-64. doi: 10.1289/ehp.1003265.	BACKGROUND: Perfluorochemicals (PFCs) are detectable in the general population and in the human environment, including house dust. Sources are not well characterized, but isomer patterns should enable differentiation of historical and contemporary manufacturing sources. Isomer-specific maternal-fetal transfer of PFCs has not been examined despite known developmental toxicity of perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) in rodents.OBJECTIVES: We elucidated relative contributions of electrochemical (phased out in 2001) and telomer (contemporary) PFCs in dust and measured how transplacental transfer efficiency (TTE; based on a comparison of maternal and cord sera concentrations) is affected by perfluorinated chain length and isomer branching pattern.METHODS: We analyzed matching samples of house dust (n = 18), maternal sera (n = 20), and umbilical cord sera (n = 20) by isomer-specific high-performance liquid chromatography tandem mass spectrometry.RESULTS: PFOA isomer signatures revealed that telomer sources accounted for 0-95% of total PFOA in house dust (median, 31%). This may partly explain why serum PFOA concentrations are not declining in some countries despite the phase-out of electrochemical PFOA. TTE data indicate that total branched isomers crossed the placenta more efficiently than did linear isomers for both PFOS (p < 0.01) and PFOA (p = 0.02) and that placental transfer of branched isomers of PFOS increased as the branching point moved closer to the sulfonate (SO3-) end of the molecule.CONCLUSIONS: Results suggest that humans are exposed to telomer PFOA, but larger studies that also account for dietary sources should be conducted. The exposure profile of PFOS and PFOA isomers can differ between the mother and fetus-an important consideration for perinatal epidemiology studies of PFCs.	●	●				●				-		B	B
110	ADME	Bogdanska, J.; Borg, D.; Bergström, U.; Mellring, M.; Bergman, Å.; Depierre, J.; Nobel, S.	Tissue distribution of 14C-labelled perfluorooctanoic acid in adult mice after 1-5 days of dietary exposure to an experimental dose or a lower dose that resulted in blood levels similar to those detected in exposed humans	2019	Chemosphere. 2020 Jan;239:124755. doi: 10.1016/j.chemosphere.2019.124755.	Perfluorooctanoic acid (PFOA), a global environmental pollutant detected in both wildlife and human populations, has several pathophysiological effects in experimental animals, including hepatotoxicity, immunotoxicity, and developmental toxicity. However, details concerning the tissue distribution of PFOA, in particular at levels relevant to humans, are lacking, which limits our understanding of how humans, and other mammals, may be affected by this compound. Therefore, we characterized the tissue distribution of 14C-PFOA in mice in the same manner as we earlier examined its analogues perfluorooctanesulfonate (PFOS) and perfluorobutanesulfonate (PFBS) in order to allow direct comparisons. Following dietary exposure of adult male C57/BL6 mice for 1, 3 or 5 days to a low dose (0.06 mg/kg/day) or a higher experimental dose (22 mg/kg/day) of 14C-PFOA, both scintillation counting and whole-body autoradiography revealed the presence of PFOA in most of the 19 different tissues examined, demonstrating its ability to leave the bloodstream and enter tissues. There were no differences in the pattern of tissue distribution with the low and high dose and the tissue-to-blood ratios were similar. At both doses, PFOA levels were highest in the liver, followed by blood, lungs and kidneys. The body compartments estimated to contain the largest amounts of PFOA were the liver, blood, skin and muscle. In comparison with our identical studies on PFOS and PFBS, PFOA reached considerably higher tissue levels than PFBS, but lower than PFOS. Furthermore, the distribution of PFOA differed notably from that of PFOS, with lower tissue-to-blood ratios in the liver, lungs, kidneys and skin.	●	●								-		B	C
111	ADME	Bogdanska, J.; Borg, D.; Sundström, M.; Bergström, U.; Halldin, K.; Abedi-Valugerdi, M.; Bergman, A.; Nelson, B.; Depierre, J.; Nobel, S.	Tissue distribution of ^{35}S-labelled perfluorooctane sulfonate in adult mice after oral exposure to a low environmentally relevant dose or a high experimental dose	2011	Toxicology. 2011 Jun 18;284(1-3):54-62. doi: 10.1016/j.tox.2011.03.014. Epub 2011 Apr 1.	The widespread environmental pollutant perfluorooctane sulfonate (PFOS), detected in most animal species including the general human population, exerts several effects on experimental animals, e.g., hepatotoxicity, immunotoxicity and developmental toxicity. However, detailed information on the tissue distribution of PFOS in mammals is scarce and, in particular, the lack of available information regarding environmentally relevant exposure levels limits our understanding of how mammals (including humans) may be affected. Accordingly, we characterized the tissue distribution of this compound in mice, an important experimental animal for studying PFOS toxicity. Following dietary exposure of adult male C57/BL6 mice for 44566 days to an environmentally relevant (0.031 mg/kg/day) or a 750-fold higher experimentally relevant dose (23 mg/kg/day) of ^{35}S-PFOS, most of the radioactivity administered was recovered in liver, bone (bone marrow), blood, skin and muscle, with the highest levels detected in liver, lungs, blood, kidney and bone (bone marrow). Following high daily dose exposure, PFOS exhibited a different distribution profile than with low daily dose exposure, which indicated a shift in distribution from the blood to the tissues with increasing dose. Both scintillation counting (with correction for the blood present in the tissues) and whole-body autoradiography revealed the presence of PFOS in all 19 tissues examined, with identification of thymus as a novel site for localization for PFOS and bone (bone marrow), skin and muscle as significant body compartments for PFOS. These findings demonstrate that PFOS leaves the bloodstream and enters most tissues in a dose-dependent manner.	●	●		●	●				●	-		A	B
112	ADME	Borg, D.; Bogdanska, J.; Sundström, M.; Nobel, S.; Håkansson, H.; Bergman, Å.; Depierre, J. W.; Halldin, K.; Bergström, U.	Tissue distribution of (35)S-labelled perfluorooctane sulfonate (PFOS) in C57Bl/6 mice following late gestational exposure	2010	Reprod Toxicol. 2010 Dec;30(4):558-65. doi: 10.1016/j.reprotox.2010.07.004. Epub 2010 Jul 23.	Exposure of rodents in utero to perfluorooctane sulfonate (PFOS) impairs perinatal development and survival. Following intravenous or gavage exposure of C57Bl/6 mouse dams on gestational day (GD) 16 to (35)S-PFOS (12.5mg/kg), we determined the distribution in dams, fetuses (GD18 and GD20) and pups (postnatal day 1, PND1) employing whole-body autoradiography and liquid scintillation counting. In dams, levels were highest in liver and lungs. After placental transfer, (35)S-PFOS was present on GD18 at 44595 times higher levels in lungs, liver and kidneys than in maternal blood. In PND1 pups, levels in lungs were significantly higher than in GD18 fetuses. A heterogeneous distribution of (35)S-PFOS was observed in brains of fetuses and pups, with levels higher than in maternal brain. This first demonstration of substantial localization of PFOS to both perinatal and adult lungs is consistent with evidence describing the lung as a target for the toxicity of PFOS at these ages.	●	●		●	●				●	-		A	B
113	ADME	Burkemper, J. L.; Aweda, T. A.; Rosenberg, A. J.; Lunderberg, D. M.; Peaslee, G. F.; Lapi, S. E.	Radiosynthesis and biological distribution of F-18-labeled perfluorinated alkyl substances	2017	Environ Sci Technol Lett. 4 (6),211-215, doi: 10.1021/acs.estlett.7b00042	A novel method for radiolabeling perfluorinated alkyl substances (PFAS) with fluorine 18 has been developed, and after purification, the stability and biological distribution in healthy mice were evaluated. Three PFAS, [F-18]PFOA (C8), [F-18]PFHxA (C6), and [F-18]PFBA (C4), were readily labeled and isolated in average yields between 12 and 31%. The stability of each compound was monitored in 0.001 ammonium hydroxide (NH4OH) in methanol, in saline, and in human, mouse, and rat sera. The amount of intact, radiolabeled PFAS was determined by radiometric instant thin layer chromatography and was calculated by the amount of free fluorine 18 observed over time. All compounds were highly stable in 0.001 NH4OH in methanol and saline, with <10% defluorination observed after 4 h. Interestingly, each compound had differing affinities for the serum proteins. In vivo biodistribution studies in mice showed uptake in all organs examined, with the highest uptake being exhibited in the liver for both [F-18]PFOA and [F-18]PFHxA and the stomach for [F-18]PFBA. The results of this initial study suggest that this method could be valuable in helping to determine the biological uptake of any PFAS in mammals.	●									-		C	B
114	ADME	Li, J.; Cai, D.; Chu, C.; Li, Q. Q.; Zhou, Y.; Hu, L. W.; Yang, B. Y.; Dong, G. H.; Zeng, X. W.; Chen, D.	High trans-placental transfer of perfluoroalkyl substances alternatives in the matched maternal-cord blood serum: Evidence from a birth cohort study	2020	Sci Total Environ. 2020 Feb 25;705:135885. doi:10.1016/j.scitotenv.2019.135885. Epub 2019 Dec 2.	Previous studies demonstrated that per- and polyfluoroalkyl substances (PFASs) can cross the human placental barrier. However, their transplacental transfer efficiencies (TTEs) have not been investigated in preterm delivery, and the role of placental transport proteins has rarely been explored. Our study hypothesized that the TTEs of PFASs could differ between preterm and full-term deliveries, and some placental transporters could be involved in active maternofetal PFAS transfer. In the present study, the median TTEs of 16 individual PFAS chemicals or isomers were determined to be 0.23 to 1.72 in matched maternal-cord serum pairs with preterm delivery (N = 86), which were significantly lower than those (0.35 to 2.26) determined in full-term delivery (N = 187). Significant associations were determined between the TTEs of several PFASs and the mRNA expression levels of selected transporters located on the brush border membrane. The association patterns also significantly differed between preterm and full-term deliveries and exhibited a chemical-specific manner. For example, the expression of MRP2 exhibited significantly positive associations with the TTEs of linear and branched perfluorooctanesulfonic acid (PFOS) isomers in full-term delivery, but negative, nonsignificant associations were observed in preterm delivery. This is the first study to compare the transplacental transfer of PFASs between preterm and full-term deliveries and indicate that some placental transport proteins could be involved in active transmission. The mechanisms underlying the cross-placental transfer of PFASs require further investigations to better elucidate their risks to fetal health and birth outcomes.	●	●								-		C	A

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
115	ADME	Chen, F.; Yin, S.; Kelly, B. C.; Liu, W.	Isomer-specific transplacental transfer of perfluoroalkyl acids: Results from a survey of paired maternal, cord sera, and placentas	2017	Environ Sci Technol. 2017 May 16;51(10):5756-5763. doi: 10.1021/acs.est.7b00268. Epub 2017 May 1.	Currently, information regarding isomer-specific concentrations of PFHxS, PFOS, and PFOA in human placenta, and corresponding placental-maternal ratios (RPM) of these compounds does not exist. The objective of the present study was to assess the occurrence, and distribution of different PFHxS, PFOS, and PFOA isomers in maternal serum, umbilical cord serum, and placenta to gain a better understanding of transplacental transport efficiency and prenatal exposure risks. The study involved quantitative determination of isomer-specific concentrations of PFHxS, PFOS, and PFOA in samples of maternal serum (n = 32), cord serum (n = 32), and placenta (n = 32) from pregnant women in Wuhan, China. The results indicate that both linear and branched PFHxS, PFOS and PFOA can be efficiently transported across the placenta, with exposure levels ordered maternal serum > cord serum > placenta. For PFOS isomers, the concentration ratios between cord serum and maternal serum (RCM) were ordered n < iso < 4m < (3 + 5)m < 1m < ∑m2. The RPM values exhibited a similar trend for branched PFOS isomers: iso < 4m ≈ (3 + 5)m < 1m ≈ ∑m2. Conversely, PFOA isomers did not exhibit an obvious structure-activity relationship for RCM and RPM. n-PFHxS transported across the placenta to a greater extent than br-PFHxS. To the best of our knowledge, this is the first study to report the occurrence of PFHxS, PFOS, and PFOA isomers in human placenta. Further, RPM values of these compounds are reported here for the first time. The findings help to better understand the mechanisms of the placental transfer and neonatal exposure to these important contaminants of concern.	●	●		●						-		B	A
116	ADME	Chen, H.; Wang, Q.; Cai, Y.; Yuan, R.; Wang, F.; Zhou, B.	Investigation of the Interaction Mechanism of Perfluoroalkyl Carboxylic Acids with Human Serum Albumin by Spectroscopic Methods	2020	Int J Environ Res Public Health. 2020 Feb; 17(4): 1319. Published online 2020 Feb 18. doi: 10.3390/ijerph17041319	Perfluoroalkyl carboxylic acids (PFCAs) are some of the most significant pollutants in human serum, and are reported to be potentially toxic to humans. In this study, the binding mechanism of PFCAs with different carbon lengths to human serum albumin (HSA) was studied at the molecular level by means of fluorescence spectroscopy under simulated physiological conditions and molecular modeling. Fluorescence data indicate that PFCAs with a longer carbon chain have a stronger fluorescence quenching ability. Perfluorobutanoic acid (PFBA) and perfluorohexanoic acid (PFHxA) had little effect on HSA. Fluorescence quenching of HSA by perfluorooctanoic acid (PFOA) and perfluorodecanoic acid (PFDA) was a static process that formed a PFCA-HSA complex. Electrostatic interactions were the main intermolecular forces between PFOA and HSA, while hydrogen bonding and van der Waals interactions played important roles in the combination of PFDA and HSA. In fact, the binding of PFDA to HSA was stronger than that of PFOA as supported by fluorescence quenching and molecular docking. In addition, infrared spectroscopy demonstrated that the binding of PFOA/PFDA resulted in a sharp decrease in the β-sheet and α-helix conformations of HSA. Our results indicated that the carbon chain length of PFCAs had a great impact on its binding affinity, and that PFCAs with longer carbon chains bound more strongly.	●	●								-		C	B
117	ADME	Chen, Y. M.; Guo, L. H.	Fluorescence study on site-specific binding of perfluoroalkyl acids to human serum albumin	2009	Arch Toxicol. 2009 Mar;83(3):255-61. doi: 10.1007/s00204-008-0359-x. Epub 2008 Oct 15.	Binding of five perfluoroalkyl acids with human serum albumin (HSA) was investigated by site-specific fluorescence. Intrinsic fluorescence of tryptophan-214 in HSA was monitored upon addition of the chemicals. Although perfluorobutyl acid (PFBA) and perfluorobutane sulfonate (PFBS) did not cause fluorescence change, perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), and perfluorododecanoic acid (PFDoA) induced fluorescence quenching, from which binding constant of 2.7 x 10(5) M(-1) for PFOA and 2.2 x 10(4) M(-1) for PFOS was calculated. Two fluorescent probes, dansylamide (DA) and dansyl-L: -proline (DP), were employed in fluorescence displacement measurements to study the interaction at two Sudlow's binding sites. At Site I, both PFBA and PFBS displaced DA with binding constants of 1 x 10(6) M(-1) and 2.2 x 10(6) M(-1). At Site II, PFBS and PFDoA displaced DP with binding constants of 6.5 x 10(6) M(-1) and 1.2 x 10(6) M(-1), whereas PFBA did not bind. The data were compared with fatty acids to evaluate the potential toxicological effect of these environmental chemicals.	●	●		●						-		C	B
118	ADME	Cheng, W.; Ng, C. A.	Predicting relative protein affinity of novel per- and polyfluoroalkyl substances (PFASs) by an efficient molecular dynamics approach	2018	Environ Sci Technol. 2018 Jul 17;52(14):7972-7980. doi: 10.1021/acs.est.8b01268. Epub 2018 Jun 27.	With the phasing out of long-chain per- and polyfluoroalkyl substances (PFASs), production of a wide variety of alternative PFASs has increased to meet market demand. However, little is known about the bioaccumulation potential of these replacement compounds. Here, we developed a modeling workflow that combines molecular docking and molecular dynamics simulation techniques to estimate the relative binding affinity of a total of 15 legacy and replacement PFASs for human and rat liver-type fatty acid binding protein (hLFABP and rLFABP). The predicted results were compared with experimental data extracted from three different studies. There was good correlation between predicted free energies of binding and measured binding affinities, with correlation coefficients of 0.97, 0.79, and 0.96, respectively. With respect to replacement PFASs, our results suggest that EEA and ADONA are at least as strongly bound to rLFABP as perfluoroheptanoic acid (PFHpA), and as strongly bound to hLFABP as perfluorooctanoic acid (PFOA). For F-53 and F-53B, both have similar or stronger binding affinities than perfluorooctanesulfonate (PFOS). Given that interactions of PFASs with proteins (e.g., LFABPs) are important determinants of bioaccumulation potential in organisms, these alternatives could be as bioaccumulative as legacy PFASs, and are therefore not necessarily safer alternatives to long-chain PFASs.	●	●								-		B	C
119	ADME	Cheng, X.; Klaassen, C. D.	Tissue distribution, ontogeny, and hormonal regulation of xenobiotic transporters in mouse kidneys	2009	Drug Metab Dispos. 2009 Nov;37(11):2178-85. doi: 10.1124/dmd.109.027177	Kidneys play important roles in the elimination of numerous endogenous and exogenous chemicals. In recent years, at least 37 xenobiotic transporters have been identified in mammalian kidneys. Although much progress has been made, information on 14 of these transporters (ATP-binding cassette [Abc] a1, apical sodium bile acid transporter [Asbt], breast cancer resistance protein, concentrative nucleoside transporter 1, equilibrative nucleoside transporter [Ent] 2, Ent3, sodium-phosphate cotransporter [Npt] 1, Npt2a, Npt2b, Npt2c, organic anion transporter [Oat] 5, organic anion-transporting polypeptide [Oatp] 4c1, peptide transporter 2, and uric acid transporter [Urat] 1) in kidneys is quite limited. Therefore, the purpose of the present study was to examine the tissue distribution, ontogeny, and hormonal regulation of these 14 transporters in kidneys of mice. Other than in kidneys, Npt2b is also highly expressed in liver and lung, Npt2c in liver and colon, Asbt in ileum, and Abca1 in liver, lung, testis, ovary, and placenta of mice. Most of these (13 of 14) transporters are lowly expressed in mouse kidneys until 15 days of age, which in part contributes to the immaturity of excretory function in fetal and newborn kidneys. One exception is Ent2, which is highly expressed before birth and gradually decreases after birth until reaching adult levels at 15 days of age. Gender-divergent expression of male-predominant (Urat1 and Oatp4c1) and female-predominant (Oat5) transporters in mouse kidneys is primarily due to stimulatory effects of androgens and estrogens, respectively. In conclusion, the mRNA expression of xenobiotic transporters in kidneys is determined by tissue, age, and sex hormones.	●	●								-		C	C
120	ADME	Cheng, X.; Maher, J.; Lu, H.; Klaassen, C. D.	Endocrine regulation of gender-divergent mouse organic anion-transporting polypeptide (Oatp) expression	2006	Mol Pharmacol. 2006 Oct;70(4):1291-7. doi: 10.1124/mol.106.025122. Epub 2006 Jun 28.	Several examples of gender-divergent pharmacokinetics exist in humans and experimental animals, and one reason for these variations may be gender differences in transporter expression. Organic anion transporting polypeptides (Oatp) are transporters involved in hepatic and renal uptake of many organic compounds. In mouse livers, Oatp1a1 is male-predominant, whereas Oatp1a4 is female-predominant. However, in kidneys, Oatp1a1 and Oatp3a1 are both female-predominant. The purpose of the present study was to determine whether sex hormones and/or growth hormone (GH) secretion patterns are responsible for the gender-specific Oatp expression in mice. Gonadectomized mice, GH-releasing hormone receptor-deficient little (lit/lit) mice, and hypophysectomized mice were used with replacement of sex hormones or GH in male or female secretion patterns. Androgens increased Oatp1a1 mRNA in liver and kidney, whereas male-pattern GH administration increased Oatp1a1 mRNA in livers but not in kidneys. Hepatic Oatp1a4 mRNA levels were decreased by both androgens and male-pattern GH administration. In kidneys, Oatp3a1 mRNA expression was only induced by androgen treatment. In conclusion, gender-divergent Oatp expression in liver is caused by male-pattern GH secretion pattern and androgens. In kidney, gender-divergent Oatp expression is exclusively caused by stimulation by androgens.	●	●								-		C	C
121	ADME	Cropp, C, .D.; Komori, T, .; Shima, J, .E.; Urban, T, .J.; Yee, S, .W.; More, S, .S.; Giacomini, K, .M.	Organic anion transporter 2 (SLC22A7) is a facilitative transporter of cGMP	2008	Mol Pharmacol. 2008 Apr;73(4):1151-8. doi: 10.1124/mol.107.043117. Epub 2008 Jan 23.	The second messenger, cGMP, mediates a host of cellular responses to various stimuli, resulting in the regulation of many critical physiologic functions. The existence of specific cGMP transporters on the plasma membrane that participate in the regulation of cGMP levels has been suggested in a large number of studies. In this study, we identified a novel plasma membrane transporter for cGMP. In particular, we showed that hOAT2 (SLC22A7), a member of the solute carrier (SLC) superfamily, was a facilitative transporter for cGMP and other guanine nucleotides. hOAT2, which is ubiquitously expressed at high levels in many cell types, was previously thought to primarily transport organic anions. Among purine and pyrimidine nucleobases, nucleosides, and nucleotides, hOAT2 showed the greatest preference for cGMP, which transported cGMP with a K(m) value of 88 +/- 11 muM and exhibited between 50- and 100-fold enhanced uptake over control cells. Our data revealed that hOAT2 is a bidirectional facilitative transporter that can control both intracellular and extracellular levels of cGMP. In addition, we observed that a common alternatively spliced variant of hOAT2 demonstrated a complete loss of transport function as a result of a low expression level on the plasma membrane. We conclude that hOAT2 is a highly efficient, facilitative transporter of cGMP and may be involved in cGMP signaling in many tissues. Our study suggests that hOAT2 represents a potential new drug target for regulating cGMP levels.	●	●								-		C	C
122	ADME	Cui, L.; Liao, C. Y.; Zhou, Q. F.; Xia, T. M.; Yun, Z. J.; Jiang, G. B.	Excretion of PFOA and PFOS in male rats during a subchronic exposure	2010	Arch Environ Contam Toxicol. 2010 Jan;58(1):205-13. doi: 10.1007/s00244-009-9336-5. Epub 2009 May 26.	Perfluorinated compounds (PFCs), a class of synthetic surfactants that are widely used, have become global environmental contaminants because of their high persistence and bioaccumulation. An increasing number of studies have described the pharmacokinetics of PFCs following in vivo exposure, however, few papers have focused on the excretion of these compounds during a period of consecutive exposure. In this study, the excretions of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) in male Sprague-Dawley rats gavaged consecutively for 28 days were investigated and compared. The faster elimination rate in urine compared to feces indicated that urinary excretion is the primary clearance route in rats for either PFOA or PFOS. During the first 24 h after administration of PFOA (5 and 20 mg/kg body weight/day), about 24.7-29.6% of the oral dose was excreted through urine and feces, while for PFOS, the excretion amounts were only 2.6-2.8% of the total gavaged doses (5 and 20 mg/kg body weight/day). The excretion rates of both PFCs increased with increasing exposure doses. The higher elimination rate of PFOA through excretion indicated its lower accumulation in rats, thus inducing possible lower toxicities compared to PFOS.	●	●			●	●				-		B	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献ラン①①	文献ラン②②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
123	ADME	D'Alessandro, M. L.; Ellis, D. A.; Carter, J. A.; Stock, N. L.; March, R. E.	Competitive binding of aqueous perfluorooctanesulfonic acid and ibuprofen with bovine serum albumin studied by electrospray ionization mass spectrometry	2013	International Journal of Mass Spectrometry. Volumes 345–347, 1 July 2013, Pages 28-36, doi: 10.1016/j.ijms.2012.12.012	Serum albumin binds reversibly with and transports endogenous and exogenous ligands, such as pharmaceuticals, whose therapeutic efficacy is activated upon liberation from the protein. Aqueous perfluorooctanesulfonic acid is a bioaccumulative, pervasive species of anthropogenic origin found in the serum of 90% of Americans that adventitiously binds with high affinity to serum albumin in the same specific site as ibuprofen; thus the conditions for competitive binding are established. This study investigated the competitive interaction between aqueous perfluorooctanesulfonic acid and ibuprofen in binding to bovine serum albumin (BSA) using electrospray ionization mass spectrometry. Perfluorooctanesulfonate was found to displace all bound ibuprofen from BSA and to prevent further ibuprofen binding when the fluorinated analyte concentration exceeds half that of ibuprofen. These observations imply that perfluorooctanesulfonate may displace ibuprofen and similar pharmaceuticals from serum albumin in the body under physiological conditions thus altering the pharmacokinetics and deposition of such drugs.	●									-		D	D
124	ADME	Davies, B.; Morris, T.	Physiological parameters in laboratory animals and humans [Review]	1993	Pharm Res. 1993 Jul;10(7):1093-5. doi: 10.1023/a:1018943613122.	No abstract available	●	●		●						書籍		D	D
125	ADME	Dourson M; Gadagbui B	The Dilemma of perfluorooctanoate (PFOA) human half-life	2021	Regul Toxicol Pharmacol. 2021 Nov;126:105025. doi: 10.1016/j.yrtph.2021.105025.	Disparity in the results from human observational and clinical studies is not uncommon, but risk assessment efforts often judge one set of data more relevant with the loss of valuable information. The assessment for perfluorooctanoate (PFOA) is a good example of this problem. The estimation of its safe dose is disparate among government groups due in part to differences in understanding of its half-life in humans. These differences are due in part to incomplete information on sources of exposure in the human observational half-life studies, which have been routinely acknowledged, but until recently not well understood. Exposure information is thus critical in understanding, and possibly resolving, this disparity in PFOA safe dose, and potentially for disparities with similar chemistries when both human observational and clinical findings are available. We explore several hypotheses to explain this disparity in PFOA half-life from human observational studies in light of findings of a clinical study in humans and relevant exposure information from a recent international meeting of the Society of Toxicology and Environmental Chemistry (SETAC). Based on information from both human observational studies and clinical data, we proposed a range for the half-life for PFOA of 0.5-1.5 years, which would likely raise many existing regulatory safe levels if all other parameters stayed the same.	●	●							●	-	1	A	A
126	ADME	Dourson, M. L.; Gadagbui, B.; Onyema, C.; Mcginnis, P. M.; York, R. G.	Data derived Extrapolation Factors for developmental toxicity: A preliminary research case study with perfluorooctanoate (PFOA)	2019	Regul Toxicol Pharmacol. 2019 Nov;108:104446. doi: 10.1016/j.yrtph.2019.104446. Epub 2019 Aug 16.	Guidelines of the United States Environmental Protection Agency (EPA, 1991) and the International Programme on Chemical Safety (IPCS, 2005) suggest two different default positions for dosimetric extrapolation from experimental animals to humans when the dosimetry of the critical effect is not known. The default position of EPA -1991 for developmental toxicity is to use peak concentration (or Cmax) for this dosimetric extrapolation. In contrast, IPCS (2005, page 39) states its default position for dosimetric choice in the absence of data is to use the area under the curve (or AUC). The choice of the appropriate dose metric is important in the development of either a Chemical Specific Adjustment Factor (CSAF) of IPCS -2005 or a Data Derived Extrapolation Factor (DDEF) of EPA (2014). This research shows the derivation of a DDEF for developmental toxicity for perfluorooctanoate (PFOA), a chemical of current interest. Here, identification of the appropriate dosimetric adjustment from a review of developmental effects identified by EPA -2016 is attempted. Although some of these effects appear to be related to Cmax, most appear to be related to the average concentration or its AUC, but only during the critical period of development for a particular effect. A comparison was made of kinetic data from PFOA exposure in mice with newly available and carefully monitored kinetic data in humans after up to 36 weeks of PFOA exposure in a phase 1 clinical trial by Elcombe et al. (2013). Using the average concentration during the various exposure windows of concern, the DDEF for PFOA was determined to be 1.3 or 14 These values are significantly different than comparable extrapolations by several other authorities based on differences in PFOA half-life among species. Although current population exposures to PFOA are generally much lower than both the experimental animal data and the clinical human study, the development of these DDEFs is consistent with current guidelines of both EPA -2014 and IPCS (2005).	●	●							●	-		B	B
127	ADME	Ebert, A.; Allendorf, F.; Berger, U.; Goss, K. U.; Ulrich, N.	Membrane/water partitioning and permeabilities of perfluoroalkyl acids and four of their alternatives and the effects on toxicokinetic behavior	2020	Environ Sci Technol. 2020 Apr 21;54(8):5051-5061. doi: 10.1021/acs.est.0c00175. Epub 2020 Apr 6.	The search for alternatives to bioaccumulative perfluoroalkyl acids (PFAAs) is ongoing. New, still highly fluorinated alternatives are produced in hopes of reducing bioaccumulation. To better estimate this bioaccumulative behavior, we performed dialysis experiments and determined membrane/water partition coefficients, Kmem/w, of six perfluoroalkyl carboxylic acids (PFCAs), three perfluoroalkanesulfonic acids, and four alternatives. We also investigated how passive permeation might influence the uptake kinetics into cells, measuring the passive anionic membrane permeability Pion through planar lipid bilayers for six PFAAs and three alternatives. Experimental Kmem/w and Pion were both predicted well by the COSMO-RS theory (log RMSE 0.61 and 0.46, respectively). Kmem/w values were consistent with the literature data, and alternatives showed similar sorption behavior as PFAAs. Experimental Pion values were high enough to explain observed cellular uptake by passive diffusion with no need to postulate the existence of active uptake processes. However, predicted pKa and neutral permeabilities suggest that also the permeation of the neutral species should be significant in case of PFCAs. This can have direct consequences on the steady-state distribution of PFAAs across cell membranes and thus toxicity. Consequently, we propose a model to predict pH-dependent baseline toxicity based on Kmem/w, which considers the permeation of both neutral and anionic species.	●	●								-		C	B
128	ADME	Fàbrega, F.; Kumar, V.; Benfenati, E.; Schuhmacher, M.; Domingo, J. L.; Nadal, M.	Physiologically based pharmacokinetic modeling of perfluoroalkyl substances in the human body	2015	Toxicol Environ Chem. 97: 814-827. doi:10.1080/02772248.2015.1060976	Currently, there are limited data on the levels of perfluoroalkyl substances other than perfluorooctane sulfonic acid and perfluorooctanoic acid in the human body. Most of this information has been extracted from biological monitoring of plasma while the occurrence of perfluoroalkyl substances in other human tissues is rarely studied. The objective of the present study was to develop a physiologically based pharmacokinetic model to assess the concentration of perfluoroalkyl substances in human tissues, based on an existing model previously validated for perfluorooctane sulfonic acid and perfluorooctanoic acid. Experimental data on concentrations of perfluoroalkyl substances in human tissues from individuals in Tarragona County (Catalonia, Spain) were used to estimate the values of some distribution and elimination parameters needed for the simulation. No significant correlations were found between these parameters and the chain lengths. The model was finally validated for five perfluoroalkyl substances.	●	●								-		B	B
129	ADME	Fenton, Suzanne E; Reiner, Jessica L; Nakayama, Shoji F; Delinsky, Amy D; Stanko, Jason P; Hines, Erin P; White, Sally S; Lindstrom, Andrew B; Strynar, Mark J; Petropoulou, Syrago-Styliani E	Analysis of PFOA in dosed CD-1 mice	2009	Reprod Toxicol. 2009 Jun;27(3-4):365-372. doi: 10.1016/j.reprotox.2009.02.012. Epub 2009 Mar 9.	Previous studies in mice with multiple gestational exposures to perfluorooctanoic acid (PFOA) demonstrate numerous dose dependent growth and developmental effects which appeared to worsen if offspring exposed in utero nursed from PFOA-exposed dams. To evaluate the disposition of PFOA in the pregnant and lactating dam and her offspring, time-pregnant CD-1 mice received a single 0, 0.1, 1, or 5mg PFOA/kg BW dose (n=25/dose group) by gavage on gestation day 17. Maternal and pup fluids and tissues were collected over time. Pups exhibited significantly higher serum PFOA concentrations than their respective dams, and their body burden increased after birth until at least postnatal day 8, regardless of dose. The distribution of milk:serum PFOA varied by dose and time, but was typically in excess of 0.20. These data suggest that milk is a substantial PFOA exposure route in mice and should be considered in risk assessment modeling designs for this compound.	●	●		●		●			●	-		A	B
130	ADME	Fernandez, E.,.; Perez, R.,.; Hernandez, A.,.; Tejada, P.,.; Arteta, M.,.; Ramos, J.,.T.	Factors and Mechanisms for Pharmacokinetic Differences between Pediatric Population and Adults	2011	Pharmaceutics. 2011 Feb 7;3(1):53-72. doi: 10.3390/pharmaceutics3010053.	Many physiologic differences between children and adults may result in age-related changes in pharmacokinetics and pharmacodynamics. Factors such as gastric pH and emptying time, intestinal transit time, immaturity of secretion and activity of bile and pancreatic fluid among other factors determine the oral bioavailability of pediatric and adult populations. Anatomical, physiological and biochemical characteristics in children also affect the bioavailability of other routes of administration. Key factors explaining differences in drug distribution between the pediatric population and adults are membrane permeability, plasma protein binding and total body water. As far as drug metabolism is concerned, important differences have been found in the pediatric population compared with adults both for phase I and phase II metabolic enzymes. Immaturity of glomerular filtration, renal tubular secretion and tubular reabsorption at birth and their maturation determine the different excretion of drugs in the pediatric population compared to adults.	●	●								-		C	C
131	ADME	Forsthuber, M.; Kaiser, A. M.; Granitzer, S.; Hassl, I.; Hengstschläger, M.; Stangl, H.; Gundacker, C.	Albumin is the major carrier protein for PFOS, PFOA, PFHxS, PFNA and PFDA in human plasma	2020	Environ Int. 2020 Apr;137:105324. doi: 10.1016/j.envint.2019.105324. Epub 2020 Feb 25.	Perfluoroalkyl (PFAS) substances are widespread in the environment and in organisms. The fact that exposure to PFAS is associated with elevated cholesterol levels is a major concern for human health. Previous investigations, in which bovine serum albumin was frequently studied, indicate that PFOS, PFOA and PFNA bind to serum albumin. However, it is critical to know whether these and other PFAS have a preference for the protein or the lipid fraction in native human blood fractions. For this reason, blood samples from four young healthy volunteers (two women, two men, 23–31 years old) were used for protein size separation and fractionation by the Cohn method in combination with serial ultracentrifugation. The plasma fractions were analyzed for 11 PFAS using high-performance tandem mass spectrometry (HPLC-MS/MS). Although the data are based on a small sample, they clearly show that albumin is the most important carrier protein for PFOS, PFOA, PFHxS, PFNA and PFDA in native human plasma. These five compounds have very little or no affinity for lipoproteins. The confirmation of their transport through albumin is important for the epidemiology of PFAS. The present results must be verified by the examination of a larger number of persons.	●	●								-		B	A
132	ADME	Fujii, Y.; Harada, K. H.; Kobayashi, H.; Haraguchi, K.; Koizumi, A.	Lactational transfer of long-chain perfluorinated carboxylic acids in mice: A method to directly collect milk and evaluate chemical transferability	2020	Toxics. 2020 Apr 1;8(2):23. doi: 10.3390/toxics8020023.	Perfluoroalkyl carboxylic acids (PFCAs), such as perfluorooctanoic acid (PFOA, C8), are a group of industrial chemicals that are detected in the serum of people throughout the world. Long-chain PFCAs (C9 to C13) have high lipophilicity, therefore they may have a high transfer rate to breast milk. This study investigated the lactational transfer of PFCAs with carbon chain lengths of 8 to 13 in mice. Lactating dams were given a single intravenous administration of PFCAs (C8 to C13) during the postnatal period (8-13 days after delivery). Milk was collected from the dam 24 h after administration using a milking device built in-house. Plasma was obtained from the dam at the same time as milk collection. The observed milk/plasma (M/P) concentration ratios were 0.32 for C8, 0.3 for C9, 0.17 for C10, 0.21 for C11, 0.32 for C12, and 0.49 for C13. These results indicate that the M/P concentration ratio is not related to the lipophilicity of PFCAs. However, estimated relative daily intake, an indicator of how much PFCA is transferred from dams to pups per body weight, increased with chain length: 4.16 for C8, 8.98 for C9, 9.35 for C10, 9.51 for C11, 10.2 for C12, and 10.49 for C13, which may be related to the lower clearance of long-chain PFCAs. These results indicate the importance of future risk assessment of long-chain PFCAs.	●	●								-		B	B
133	ADME	Gabrielsson, J; Weiner, D.	Pharmacokinetic and pharmacodynamic data analysis: concepts and applications (3rd ed)	2000	Stockholm: Swedish Pharmaceutical Press.	No abstract available	●									-		D	D

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報収集対象	文献ランク①	文献ランク②
134	ADME	Gannon, Shawn A; Fasano, William J; Mawn, Michael P; Nabb, Diane L; Buck, Robert C; Buxton, L William; Jepson, Gary W; Frame, Steven R	Absorption, distribution, metabolism, excretion, and kinetics of 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)propanoic acid ammonium salt following a single dose in rat, mouse, and cynomolgus monkey	2016	Toxicology. 2016 Jan 18;340:1-9. doi: 10.1016/j.tox.2015.12.006. Epub 2015 Dec 29.	Ammonium, 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)-propanoate has been developed as a processing aid used in the manufacture of fluoropolymers. The absorption, distribution, elimination, and distribution (ADME) and kinetic behavior of this substance has been evaluated in rats, mice, and cynomolgus monkeys by oral and intravenous routes of exposure and studied in both plasma and urine. The test substance is rapidly and completely absorbed in both rats and mice and both in vivo and in vitro experiments indicate that it is not metabolized. The test substance is rapidly eliminated exclusively in the urine in both rats and mice, with rats eliminating it more quickly than mice (approximately 5h elimination half-life in rats, 20 h half-life in mice). Pharmacokinetic analysis in monkeys, rats, and mice indicate rapid, biphasic elimination characterized by a very fast alpha phase and a slower beta phase. The beta phase does not contribute to potential accumulation after multiple dosing in rats or monkeys. Comparative pharmacokinetics in rats, mice, and monkeys indicates that the rat is more similar to the monkey and is therefore a more appropriate rodent model for pharmacokinetics in primates.	●	●								-		C	C
135	ADME	Gao, B.; He, X.; Liu, W.; Zhang, H.; Saito, N.; Tsuda, S.	Distribution of perfluoroalkyl compounds in rats: Indication for using hair as bioindicator of exposure	2015	J Expo Sci Environ Epidemiol. 2015 Nov-Dec;25(6):632-8. doi: 10.1038/jes.2014.54. Epub 2014 Aug 13.	Hair analysis is potentially advantageous in exposure assessment of perfluoroalkyl acids (PFAAs) as a non-invasive method, combined with the ability to reflect long-term exposure. The present study aims to assess the feasibility of using hair as an indicator of PFAA exposure. Adult male and female rats were subchronically exposed to selected PFAAs, including perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), and perfluorooctanesulfonate (PFOS), for 90 days. Hair, serum, and other tissues, including liver, kidney, spleen, lung, brain and heart, as well as the urine and feces excretions, were analyzed for PFAA levels. PFOA/PFNA/PFOS were detected in rat hair in a dose-dependent manner, in the order of PFOS>PFNA>PFOA. Hair PFAA concentrations were higher in male rats than the female rats, except for PFOS at low dose. Moreover, significant positive correlations as well as similar PFAA profiles were observed between hair, serum, and other tissues. Besides, hair PFAAs were negatively correlated with the urinary excretion rate. Although the influencing factors in humans still need further investigation, the results suggested that hair is capable of reflecting PFAA exposure, and could be employed as an alternative exposure bioindicator of PFAAs.Journal of Exposure Science and Environmental Epidemiology advance online publication, 13 August 2014; doi:10.1038/jes.2014.54.	●	●		●						-		B	B
136	ADME	Genuis, S. J.; Birkholz, D.; Ralitsch, M.; Thibault, N.	Human detoxification of perfluorinated compounds	2010	Public Health. 2010 Jul;124(7):367-75. doi: 10.1016/j.puhe.2010.03.002.	There has been no proven method thus far to accelerate the clearance of potentially toxic perfluorinated compounds (PFCs) in humans. PFCs are a family of commonly used synthetic compounds with many applications, including repelling oil and stains on furniture, clothing, carpets and food packaging, as well as in the manufacturing of polytetrafluoroethylene - a non-stick surfacing often used in cookware (e.g. Teflon(r)). Some PFCs remain persistent within the environment due to their inherent chemical stability, and are very slowly eliminated from the human body due, in part, to enterohepatic recirculation. Exposure to PFCs is widespread and some subpopulations, living in proximity to or working in fluorochemical manufacturing plants, are highly contaminated. PFC bioaccumulation has become an increasing public health concern as emerging evidence suggests reproductive toxicity, neurotoxicity and hepatotoxicity, and some PFCs are considered to be likely human carcinogens. A case history is presented where an individual with high concentrations of PFCs in serum provided: -1 sweat samples after use of a sauna; and -2 stool samples before and after oral administration of each of two bile acid sequestrants - cholestyramine (CSM) and saponin compounds (SPCs). Stool samples before and after use of a cation-exchange zeolite compound were also examined. PFCs found in serum were not detected in substantial quantities in sweat or in stool prior to treatment. Minimal amounts of perfluorooctanoic acid, but no other PFCs, were detected in stool after SPC use; minimal amounts of perfluorooctanesulfonate, but no other PFCs, were detected in stool after zeolite use. All PFC congeners found in serum were detected in stool after CSM use. Serum levels of all PFCs subsequently declined after regular use of CSM. Further study is required but this report suggests that CSM therapy may facilitate gastrointestinal elimination of some PFCs from the human body.	●					●			●	-		B	C
137	ADME	Genuis, S. J.; Liu, Y.; Genuis, Q. I.; Martin, J. W.	Phlebotomy treatment for elimination of perfluoroalkyl acids in a highly exposed family: a retrospective case-series	2014	PLoS ONE. 2014 Dec 12;9(12):e114295. doi: 10.1371/journal.pone.0114295. eCollection 2014.	BACKGROUND: Perfluoroalkyl acids (PFAAs) are a family of commonly used synthetic chemicals that have become widespread environmental contaminants. In human serum, perfluorohexane sulfonate (PFHxS), perfluorooctane sulfonate (PFOS), and perfluorooctanoate (PFOA) are most frequently detected, in part owing to their long elimination half-lives of between 3.8 yrs (PFOA) and 8.5 yrs (PFHxS). These PFAAs also cross the placenta and have been associated with developmental toxicity, and some are considered likely human carcinogens. Interventions to eliminate PFAAs in highly contaminated individuals would reduce future health risks, but minimal research has been conducted on methods to facilitate accelerated human clearance of these persistent substances.METHODS: Six patients with elevated serum concentrations from a single family were treated by intermittent phlebotomy over a 44656 year period at intervals similar to, or less frequent than what is done for routine blood donation at Canadian Blood Services. The apparent elimination half-life (HLapp) for PFHxS, PFOS, and PFOA in this treated population was calculated in each patient and compared to the intrinsic elimination half-lives (HLin) from a literature reference population of untreated fluorochemical manufacturing plant retirees (n = 26, age >55 yrs).RESULTS: For all three PFAAs monitored during phlebotomy, HLapp in each of the family members (except the mother, who had a low rate of venesection) was significantly shorter than the geometric mean HL measured in the reference population, and in some cases were even shorter compared to the fastest eliminator in the reference population.CONCLUSION: This study suggests significantly accelerated PFAA clearance with regular phlebotomy treatment, but the small sample size and the lack of controls in this clinical intervention precludes drawing firm conclusions. Given the minimal risks of intermittent phlebotomy, this may be an effective and safe clinical intervention to diminish the body burden of PFAAs in highly exposed people.	●	●								-		C	B
138	ADME	Gibson, SJ; Johnson, JD.	Absorption of FC-143-14C in Rats After a Single Oral Dose	1979	USEPA Public Docket AR-226-0455	No abstract available	●	●			●	●				USEPA Public Docket AR-226-0455で検索したが入手できず		D	D
139	ADME	Han, Xing; Snow, Timothy A; Kemper, Raymond A; Jepson, Gary W	Binding of perfluorooctanoic acid to rat and human plasma proteins	2003	Chem Res Toxicol. 2003 Jun;16(6):775-81. doi: 10.1021/tx034005w.	Perfluorooctanoic acid (PFOA) is a commercially important organic fluorochemical and is considered to have a long half-life in human blood. In this paper, PFOA binding to rat and human plasma proteins was investigated. On the basis of results from size-exclusion chromatography and ligand blotting, most PFOA was in protein-bound form in male and female rat plasma, and the primary PFOA binding protein in plasma was serum albumin. PFOA binding to rat serum albumin (RSA) in the gas phase was observed by electrospray ionization MS. (19)F NMR experiments revealed that binding to RSA caused peak broadening and chemical shift changes of PFOA resonances, and on the basis of this observation, the dissociation constant was determined to be approximately 0.3 mM. The dissociation constants for PFOA binding to RSA and human serum albumin (HSA) and the numbers of PFOA binding sites on RSA and HSA were also determined by a separation method using microdesalting columns. No significant difference was found between PFOA binding to RSA and PFOA binding to HSA. The dissociation constants for binding of PFOA to RSA or HSA and the numbers of PFOA binding sites were in the range of 0.3-0.4 mM and 6-9, respectively. On the basis of these binding parameters and the estimated plasma concentration of serum albumin, greater than 90% of PFOA would be bound to serum albumin in both rat and human blood.	●	●		●		●				-		B	B
140	ADME	Hanhijärvi, H; Ophaug, R H; Singer, L	THE SEX-RELATED DIFFERENCE IN PERFLUOROOCTANOATE EXCRETION IN THE RAT	1982	Proc Soc Exp Biol Med. 1982 Oct;171(1):50-5. doi: 10.3181/00379727-171-41476.	No abstract available	●			●								D	D
141	ADME	Harkness, JE; Wagner, JE.	The Biology and Medicine of Rabbits and Rodents (2nd ed)	1983	Philadelphia, PA: Lea & Febiger.	No abstract available	●	●								書籍		D	D
142	ADME	Hinderliter, P M; DeLorme, M P; Kennedy, G L	Perfluorooctanoic acid: Relationship between repeated inhalation exposures and plasma PFOA concentration in the rat	2006	Toxicology. 2006 May 1;222(1-2):80-5. doi: 10.1016/j.tox.2006.01.029. Epub 2006 Mar 2.	A large database exists describing the pharmacokinetic behavior of perfluorooctanoic acid (PFOA) following oral exposure. The objective of this study was to examine the concentration- and time-dependence of the pharmacokinetics of inhaled PFOA in rats to determine equivalent inhalation and oral (from literature values) exposure levels. The study was comprised of two separate experiments: a single 6-h inhalation exposure and repeated inhalation exposures for 3 weeks (6h per day, 5 days per week). In both experiments, male and female rats were exposed nose-only to aerosol atmospheres of either 0, 1, 10, or 25mg/m(3) PFOA. In the single exposure experiment, blood was drawn via the tail vein pre-exposure, four times concurrent to exposure, and six times post-exposure up to 24h. In the repeated exposure experiment, blood was collected immediately before and after exposure 3 days per week. Plasma PFOA concentrations were quantitated by liquid chromatography-mass spectrometry (LC-MS). Following the single exposures, plasma PFOA concentrations were directly proportional to airborne concentrations in both male and female rats. Elimination of PFOA from the plasma was sex-dependent, with female rats eliminating PFOA much more rapidly than male rats. Following repeated PFOA exposure, there was little daily PFOA carryover observed in plasma samples from female rats, while males demonstrated an accumulative pattern over the 3-week period. Peak post-exposure PFOA plasma concentrations in female rats averaged 1, 2, and 4 microg/mL when exposed to 1, 10, and 25mg/m(3) PFOA, respectively, and returned to baseline levels by the time of the next pre-exposure sample collection. Male rats reached steady state plasma concentrations of 8, 21, and 36 microg/mL (ppm) after 3 weeks of exposure to 1, 10, and 25mg/m(3) PFOA, respectively. These results demonstrate that the pharmacokinetic properties of inhaled PFOA in male and female rats are similar to those observed in male and female rats following oral dosing with PFOA. It is thus possible to use this internal dose metric (plasma PFOA) for route-to-route dose extrapolation, with inhalation exposures of 1, 10, and 25mg/m(3) PFOA corresponding to oral doses of approximately 0.3, 1.0, and 2.0mg/kg in rats.	●	●		●					●	-		A	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報収集対象抽出	文献ランク①	文献ランク②
143	ADME	Hinderliter, P. M.; Han, X.; Kennedy, G. L.; Butenhoff, J. L.	Age effect on perfluorooctanoate (PFOA) plasma concentration in post-weaning rats following oral gavage with ammonium perfluorooctanoate (APFO)	2006	Toxicology. 2006 Aug 15;225(2-3):195-203. doi: 10.1016/j.tox.2006.06.002. Epub 2006 Jun 9.	The relationship between age and plasma concentration of perfluorooctanoate (PFOA) in young rats was investigated. The study was conducted in two phases in which male and female rats between 3 and 8 weeks of age were administered the ammonium salt of PFOA (APFO) by single oral gavage at either 10 or 30mg/kg. In Phase I, APFO was administered at a dose of 10mg/kg body weight to 27-, 34-, 38-, 48-, and 55-day-old male and female rats. Plasma was collected 24h after the dose. In Phase II, APFO doses of either 10 or 30mg/kg body weight were given to groups of 23-, 30-, and 32-day-old male and female rats, and plasma was collected at 2 and 24h after the dose (separate groups), and urine was collected for 24h. PFOA concentrations were measured by LC/MS/MS. In Phase I, plasma concentrations of PFOA were not dependent on age for rats 5 weeks of age and older; however, in 4-week-old rats, male plasma PFOA concentrations were 5-6 times lower than during weeks 5-8, and female plasma PFOA concentrations were 2.5-4 times higher than subsequent weeks. In Phase II, plasma samples collected 2h post-dosing indicated no significant difference in the PFOA uptake by age in females; although, in males, plasma PFOA concentrations were significantly less in 32-day-old rats, approximating one-half of the values observed at 23 and 30 days of age. Plasma samples collected 24h after dosing from 3- to 5-week-old rats indicated a slightly but significantly higher male plasma concentration at 30 and 32 days of age as compared to 23 days of age for the 30mg/kg dose group only. Significantly lower (approximately 10-fold) plasma PFOA concentrations occurred in 32-day-old females as compared with 23- and 30-day-old females at both 2 and 24h after the dose. Although statistically significant changes in urine PFOA concentrations did not occur between age and dose groups within sex, urine PFOA concentrations generally supported plasma elimination. At 23 days of age, the ratio of male to female plasma PFOA concentrations was approximately 2-3:1 compared to approximately 30:1 at 32 days of age. An unexplainable inconsistency in PFOA plasma concentrations for both sexes was noted when comparing Phase I values for 27-day-old rats to Phase II values for 23- and 30-day-old rats. The Phase I values for the 27-day-old rats of both sexes were five to six times lower than Phase II values for the 23- and 30-day-old rats. However, Phase I values for 34-day-old rats were comparable to Phase II values for 32-day-old rats. Despite this anomaly between the 23-, 27-, and 30-day-old rat values, there is strong evidence that age-dependent changes in the elimination of PFOA develop in female rats between 3 and 5 weeks of age, with a consistent marked difference occurring after 30 days of age.	●	●		●		●				-		B	B
144	ADME	Hinderliter, Paul M; Mylchreest, Eve; Gannon, Shawn A; Butenhoff, John L; Kennedy, Gerald L Jr	Perfluorooctanoate: Placental and lactational transport pharmacokinetics in rats	2005	Toxicology. 2005 Jul 1;211(1-2):139-48. doi: 10.1016/j.tox.2005.03.010. Epub 2005 Apr 19.	This study was conducted to develop a quantitative understanding of the potential for gestational and lactational transfer of perfluorooctanoate (PFOA) in the rat. Time-mated female rats were dosed by oral gavage once daily at concentrations of 3, 10, or 30 mg/kg/day of the ammonium salt of PFOA (APFO) starting on gestation (G) day 4 and continuing until sacrifice. On days 10, 15, and 21G, five rats per dose level were sacrificed and blood samples were collected 2h post-dose. Embryos were collected on day 10G, amniotic fluid, placentas, and embryos/fetuses were collected on days 15 and 21G, and fetal blood samples were collected on day 21G. Five rats per dose level were allowed to deliver and nurse their litters, and on days 3, 7, 14, and 21 post-partum (PP) milk and blood samples of maternal and pup were collected 2h post-dose. All samples were analyzed by high-performance liquid chromatography-mass spectrometry (HPLC-MS) for PFOA concentration. Concentrations of PFOA in maternal plasma and milk attained steady state during the sampling interval. The steady-state concentrations in maternal plasma were 10-15, 25-30, and 60-75 microg/mL in rats receiving 3, 10, and 30 mg/kg, respectively. Steady-state concentrations in milk were approximately 10 times less than those in maternal plasma. The concentration of PFOA in fetal plasma on day 21G was approximately half the steady-state concentration in maternal plasma. The milk concentrations appeared to be generally comparable to the concentrations in pup plasma. Pup plasma concentrations decreased from day 3PP to day 7PP, and were similar on days 7, 14, and 21PP at all dose levels. PFOA was detected in placenta (days 15 and 21G), amniotic fluid (days 15 and 21G), embryo (days 10 and 15G), and fetus (day 21G). These pharmacokinetics allow estimation of the dose to developing and nursing rat offspring following maternal exposure.	●	●		●		●			●	-		A	B
145	ADME	Houston, R. A.	Care of the mentally disabled in and around Edinburgh c	2003	J R Coll Physicians Edinb. 2003;33(Suppl 12):12-20.	No abstract available	●	●										D	D
146	ADME	Huang, M C; Dzierlenga, A L; Robinson, V G; Waidyanatha, S; DeVito, M J; Eifrid, M A; Granville, C A; Gibbs, S T; Blystone, C R	Corrigendum to "Toxicokinetics of perfluorobutane sulfonate (PFBS), perfluorohexane-1-sulphonic acid (PFHxS), and perfluorooctane sulfonic acid (PFOS) in male and female Hsd:Sprague Dawley SD rats after intravenous and gavage administration" [Toxicol	2021	Toxicol Rep. 2021 Feb 18;8:365. doi: 10.1016/j.toxrep.2021.02.001. eCollection 2021.	[This corrects the article DOI: 10.1016/j.toxrep.2019.06.016.]. Huang, M C Huang MC	●	●								修正論文		D	D
147	ADME	Hundley, S. G.; Sarrif, A. M.; Kennedy, G. L.	Absorption, distribution, and excretion of ammonium perfluorooctanoate (APFO) after oral administration to various species	2006	Drug Chem Toxicol. 2006;29(2):137-45. doi: 10.1080/01480540600561361.	Male and female mice, rats, hamsters, and rabbits were treated with a single oral dose of 14C-ammonium perfluorooctanoate (APFO), and the excretion and tissue distributions were followed for 120 h (168 h in the rabbit). Substantial sex and species differences in the excretion and disposition of 14C-radioactivity derived from 14C-labeled APFO were observed in this study. The female rat and the male hamster excreted more than 0.99 of the original 14C activity by 120 h after dosing; conversely, the male rat and the female hamster excreted only 0.39 and 0.6 of the original 14C activity, respectively, by 120 h postdosing. The male and female rabbits excreted the 14C activity as rapidly and completely as the female rat and the male hamster, whereas male and female mice excreted only 0.21 of the original 14C activity by 120 h postdosing. The rapid excretors (female rat, male hamster, and male and female rabbits) contained negligible amounts of 14C in organs and tissues at sacrifice. The slow excretors exhibited the highest 14C concentrations in the blood and liver followed by the kidneys, lungs, and skin.	●	●		●	●	●				-		B	C
148	ADME	Ito, S.; Alcorn, J.	Xenobiotic transporter expression and function in the human mammary gland	2003	Adv Drug Deliv Rev. 2003 Apr 29;55(5):653-65. doi: 10.1016/s0169-409x(03)00031-0.	Xenobiotic transport in the mammary gland has tremendous clinical, toxicological and nutritional implications. Mechanisms such as passive diffusion, carrier-mediated transport, and transcytosis mediate xenobiotic transfer into milk. In vivo animal and human studies suggest the functional expression of both xenobiotic and nutrient transporters in the lactating mammary gland and the potential involvement of such systems in the significant accumulation of certain compounds in milk. In vitro cell culture systems provide further evidence for carrier-mediated transport across the lactating mammary epithelium. Additionally, molecular characterization studies indicate the expression of various members of the organic cation transporter, organic anion transporter, organic anion polypeptide transporter, oligopeptide transporter, nucleoside and nucleobase transporter, multidrug resistant transporter, and multidrug resistant-like protein transporter families at the lactating mammary epithelium. The in vivo relevance of the expression of such xenobiotic and nutrient transporters and their involvement in drug disposition at the mammary gland requires investigation.	●	●								-		C	C
149	ADME	James, K.; Peters, R. E.; Laird, B. D.; Ma, W. K.; Wickstrom, M.; Stephenson, G. L.; Siciliano, S. D.	Human exposure assessment: a case study of 8 PAH contaminated soils using in vitro digestors and the juvenile swine model	2011	Environ Sci Technol. 2011 May 15;45(10):4586-93. doi: 10.1021/es1039979. Epub 2011 Apr 18.	In vitro digestors can be used to provide bioaccessibility values to help assess the risk from incidental human ingestion of contaminated soils. It has been suggested that these digestors may need to include a lipid sink to mimic human uptake processes. We compare the correspondence between in vivo polycyclic aromatic hydrocarbon (PAH) uptake for eight different PAH contaminated soils with PAH release in in vitro digestors in the presence and absence of a lipid sink. Lipid sinks were essential to the success of the in vitro digestors in predicting juvenile swine PAH uptake. In the presence of the lipid sink, results of the In Vitro Digestion model (IVD) closely corresponded with a slope of 0.85 (r(2) = 0.45, P < 0.07) to the in vivo results. The Relative Bioaccessibility Leaching Procedure (RBALP) results did not correspond to the in vivo study but did tightly reflect total soil PAH concentration. We conclude that the basis of this difference between digestors is that the RBALP used an aggressive extraction technique that maximized PAH release from soil. Systemic uptake in juvenile swine was not linked to soil PAH concentration but rather to the thermodynamic properties of the soil.	●	●								-		C	C
150	ADME	Johanson, C.,. E.	Distribution of fluid between extracellular and intracellular compartments in the heart, lungs, liver and spleen of neonatal rats	1979	Biol Neonate. 1979;36(5-6):282-9. doi: 10.1159/000241241.	The volume of fluid in various tissue compartments of thoracic and abdominal viscera in neonatal rats has been calculated from the steady state distribution of radioindicators. During the first 3 weeks after birth, the volume of extracellular fluid (3H-inulin space) decreases at a similar rate (ca. 0.04 ml/g tissue/week) in heart, lungs, liver and spleen. Over the same postnatal period, the 51Cr tagged erythrocyte space (an estimate of vascularity) remains relatively constant in liver, increases slightly in the heart and spleen, and rises substantially (3-fold increase) in the lungs. The volume of parenchymal cell water, calculated from data for tissue water content and radioindicator spaces, tends to increase with age. However, the distribution of fluid between extracellular and intracellular compartments in 3-week-old animals is similar to that in adults.	●	●								-		C	C
151	ADME	Johnson, J. D.; Gibson, S. J.; Ober, R. E.	Cholestyramine-enhanced fecal elimination of c-14 in rats after administration of ammonium [c-14] perfluorooctanoate or potassium [c-14]perfluorooctanesulfonate	1984	Fundam Appl Toxicol. 1984 Dec;4(6):972-6. doi: 10.1016/0272-0590(84)90235-5.	After a single intravenous dose of ammonium [14C]perfluorooctanoate [(14C]PFO, 13.3 mg/kg) or of potassium [14C]perfluorooctanesulfonate [(14C]PFOS, 3.4 mg/kg) to rats, cholestyramine fed daily as a 0.04 mixture in feed was shown to increase the total carbon-14 eliminated via feces and to decrease liver concentration of carbon-14. Rats were fed cholestyramine in feed for 14 days after administration of [14C]PFO and for 21 days after administration of [14C]PFOS. Control rats were administered radiolabeled fluorochemical but were not treated with cholestyramine. Cholestyramine treatment increased mean cumulative carbon-14 elimination in feces by 9.8-fold for rats administered [14C]PFO and by 9.5-fold for rats administered [14C]PFOS. After [14C]PFO, a mean of 0.04 of the dose of carbon-14 was in liver of cholestyramine-treated rats at 14 days versus 0.076 in control rats; after [14C]PFOS, 0.113 of the dose was in liver at 21 days versus 0.403 in control rats. After administration of either radiolabeled compound, plasma and red blood cell carbon-14 concentrations, which were relatively lower than liver concentrations, were also significantly reduced by cholestyramine treatment.	●	●		●						-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ラン①抽出	文献ラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
152	ADME	Johnson, JD; Ober, RE.	Absorption of FC-95-14C in rats after a single oral dose	1979	3M. Submitted to the U.S. Environmental Protection Agency's Administrative Record. AR226-0007.	Renal elimination and the resulting clearance of perfluorooctanoic acid (PFOA) from the serum exhibit pronounced sex differences in the adult rat. The literature suggests that this is largely due to hormonally regulated expression of organic anion transporters (OATs) on the apical and basolateral membranes of the proximal tubule cells that facilitate excretion and reabsorption of PFOA from the filtrate into the blood. Previously developed PBPK models of PFOA exposure in the rat have not been parameterized to specifically account for transporter-mediated renal elimination. We developed a PBPK model for PFOA in the male and female rat to explore the role of Oat1, Oat3, and Oatp1a1 in sex-specific renal reabsorption and excretion of PFOA. Descriptions of the kinetic behavior of these transporters were extrapolated from in vitro studies and the model was used to simulate time-course serum, liver, and urine data for intravenous (IV) and oral exposures in both sexes. Model predicted concentrations of PFOA in the liver, serum, and urine showed good agreement with experimental data for both the male and female rat indicating that in vitro derived physiological descriptions of transporter-mediated renal reabsorption can successfully predict sex-dependent excretion of PFOA in the rat. This study supports the hypothesis that sex-specific serum half-lives for PFOA are largely driven by expression of transporters in the kidney and contributes to the development of PBPK modeling as a tool for evaluating the role of transporters in renal clearance.	●	●		●	●	●				-		B	D
153	ADME	Kang, Q.; Gao, F.; Zhang, X.; Wang, L.; Liu, J.; Fu, M.; Zhang, S.; Wan, Y.; Shen, H.; Hu, J.	Nontargeted identification of per- and polyfluoroalkyl substances in human follicular fluid and their blood-follicle transfer	2020	Environ Int. 2020 Jun;139:105686. doi: 10.1016/j.envint.2020.105686. Epub 2020 Apr 9.	The female reproductive toxicity of per- and polyfluoroalkyl substances (PFAS) has raised concerns, but knowledge about their human preconception exposure is limited. In this study, 15 emerging PFAS were identified in follicular fluid samples from healthy women by using high-resolution mass spectrometry, and Cl-substituted perfluoroalkyl ether sulfonates (Cl-PFESAs) including 4:2, 5:2, 6:2, and 8:2 Cl-PFESAs, 4:4 C8 perfluoroalkyl ether sulfonate (PFESA), C8 perfluoroalkyl ether carboxylate (PFECA), and C8 polyether PFECA (Po-PFECA) were detected in over 50% of 28 follicular fluid samples. Ten legacy PFAS were also detected, and the geometric mean concentration of PFOS was the highest (4.82 ng/mL), followed by PFOA (4.60 ng/mL), 6:2 Cl-PFESA (1.09 ng/mL), PFHxS (0.515 ng/mL), PFNA (0.498 ng/mL), and C8 PFECA (0.367 ng/mL). The blood-follicle transfer efficiencies for PFCAs decreased with increasing chain length (0.96 for PFHpA, 0.56 for PFTriDA), and the transfer efficiencies of C8 PFECA (0.78) was significantly higher than that of PFOA (0.76). The transfer efficiencies of 4:2 Cl-PFESA (0.73), 6:2 Cl-PFESA (0.75) and 8:2 Cl-PFESA (0.91) were significantly higher than that (0.70) of PFOS (p = 0.028, 0.026 and 0.002, respectively). This study constitutes the first report of the human oocyte exposure to emerging PFAS and their blood-follicle transfer abilities.	●	●								-		B	B
154	ADME	Kapraun, DF; Zurlinden, TJ; Verner, M-A; Chiang, C; Dzierlenga, MW; Carlson, LM; Schlosser, PM; Lehmann, GM.	Pharmacokinetic Models for Quantifying Mother-to-Offspring Transfer of Lipophilic Persistent Environmental Chemicals	2021	U. S. Environmental Protection Agency, https://cfpub.epa.gov/si/si_public_record_report.cfm?Lab=NCEA&dirEntryId=352291	No abstract available	●								ポスター		D	D
155	ADME	Kemper, R.	Perfluorooctanoic acid: Toxicokinetics in the rat	2003	Association of Plastics Manufactures of Europe. Project ID: DuPont 7473. U.S. EPA public docket, administrative record. AR226-1499.	No abstract available	●	●		●	●	●			USEPA Public Docket AR226-1499で検索したが入手できず		D	D
156	ADME	Kerstner-Wood, C., Coward, L. and Gorman, G.	Protein binding of perfluorobutane sulfonate, perfluorohexane sulfonate, perfluorooctane sulfonate and perfluorooctanoate to plasma (human, rat, and monkey), and various human-derived plasma protein fractions	2003	Southern Research Institute. Submitted to the U.S. Environmental Protection Agency's Administrative Record. AR226-1354.	No abstract available	●	●		●		●			USEPA Public Docket AR226-1354で検索したが入手できず		D	D
157	ADME	Kim, RB.	Organic anion-transporting polypeptide (OATP) transporter family and drug disposition [Review]	2003	Eur J Clin Invest. 33 Suppl 2: 1-5. doi: 10.1046/j.1365-2362.33.s2.5.x.	Drug transporters are increasingly recognized as a key determinant of drug disposition. Recent studies have revealed that targeted expression of drug uptake and efflux transporters to specific cell membrane domains allows for the efficient directional movement of many drugs in clinical use. While the role of certain efflux transporters such as MDR1 (P-glycoprotein) in drug disposition has been extensively studied, emerging evidence suggests that uptake transporters may also be important to the intestinal absorption and renal or hepatic elimination of drugs. Members of the organic anion-transporting polypeptide (OATP) family of drug uptake transporters have been found capable of transporting a large array of structurally divergent drugs. Moreover, expression of OATP isoforms in the gastrointestinal tract, liver and kidney, as well as at the level of the blood-brain barrier, has important implications for our understanding of the factors governing drug absorption, elimination and tissue penetration.	●	●								-		C	C
158	ADME	Kimura, O.; Fujii, Y.; Haraguchi, K.; Kato, Y.; Ohta, C.; Koga, N.; Endo, T.	Uptake of perfluorooctanoic acid by Caco-2 cells: Involvement of organic anion transporting polypeptides	2017	Toxicol Lett. 2017 Aug 5;277:18-23. doi: 10.1016/j.toxlet.2017.05.012. Epub 2017 May 25.	The mechanism underlying the intestinal absorption of perfluorooctanoic acid (PFOA) was investigated using Caco-2 cells. The uptake of PFOA from the apical membrane of Caco-2 cells was fast, and pH, temperature, and concentration dependent, but Na(+) independent. Coincubation with sulfobromophthalein (BSP), glibenclamide, estron-3-sulfate, cyclosporine A or rifamycin SV, which are typical substrates or inhibitors of organic anion transporting polypeptides (OATPs), significantly decreased the uptake of PFOA. However, coincubation with probenecid or p-aminohippuric acid, typical substrates of organic anion transporters, did not decrease the uptake of PFOA. Furthermore, coincubation with l-lactic acid or benzoic acid, substrates of monocarboxylic acid transporters, did not decrease PFOA uptake. The relationship between the initial uptake of PFOA and its concentration was saturable, suggesting the involvement of a carrier-mediated process. The calculated Km and uptake clearance (Vmax/Km) values for PFOA were 8.3μM and 55.0μL/mg protein/min, respectively. This clearance value was about 3-fold greater than that of the non-saturable uptake clearance (Kd: 18.1μL/mg protein/min). Lineweaver-Burk plots revealed that BSP competitively inhibits the uptake of PFOA, with a Ki value of 23.1μM. These results suggest that the uptake of PFOA from the apical membranes of Caco-2 cells could be, at least in part, mediated by OATPs along with BSP.	●	●								-		B	B
159	ADME	Klaassen, Curtis D; Aleksunes, Lauren M	Xenobiotic, bile acid, and cholesterol transporters: function and regulation	2010	Pharmacol Rev. 2010 Mar;62(1):1-96. doi: 10.1124/pr.109.002014. Epub 2010 Jan 26.	Transporters influence the disposition of chemicals within the body by participating in absorption, distribution, and elimination. Transporters of the solute carrier family (SLC) comprise a variety of proteins, including organic cation transporters (OCT) 1 to 3, organic cation/carnitine transporters (OCTN) 1 to 3, organic anion transporters (OAT) 1 to 7, various organic anion transporting polypeptide isoforms, sodium taurocholate cotransporting polypeptide, apical sodium-dependent bile acid transporter, peptide transporters (PEPT) 1 and 2, concentrative nucleoside transporters (CNT) 1 to 3, equilibrative nucleoside transporter (ENT) 1 to 3, and multidrug and toxin extrusion transporters (MATE) 1 and 2, which mediate the uptake (except MATEs) of organic anions and cations as well as peptides and nucleosides. Efflux transporters of the ATP-binding cassette superfamily, such as ATP-binding cassette transporter A1 (ABCA1), multidrug resistance proteins (MDR) 1 and 2, bile salt export pump, multidrug resistance-associated proteins, multidrug resistance protein, and ATP-binding cassette subfamily G members 5 and 8, are responsible for the unidirectional export of endogenous and exogenous substances. Other efflux transporters [ATPase copper-transporting beta polypeptide (ATP7B) and ATPase class I type 8B member 1 (ATP8B1) as well as organic solute transporters (OST) alpha and beta] also play major roles in the transport of some endogenous chemicals across biological membranes. This review article provides a comprehensive overview of these transporters (both rodent and human) with regard to tissue distribution, subcellular localization, and substrate preferences. Because uptake and efflux transporters are expressed in multiple cell types, the roles of transporters in a variety of tissues, including the liver, kidneys, intestine, brain, heart, placenta, mammary glands, immune cells, and testes are discussed. Attention is also placed upon a variety of regulatory factors that influence transporter expression and function, including transcriptional activation and post-translational modifications as well as subcellular trafficking. Sex differences, ontogeny, and pharmacological and toxicological regulation of transporters are also addressed. Transporters are important transmembrane proteins that mediate the cellular entry and exit of a wide range of substrates throughout the body and thereby play important roles in human physiology, pharmacology, pathology, and toxicology.	●	●								-		C	C
160	ADME	Klaassen, C.,.D.; Lu, H.,.	Xenobiotic transporters: ascribing function from gene knockout and mutation studies	2008	Toxicol Sci. 2008 Feb;101(2):186-96. doi: 10.1093/toxsci/kfm214. Epub 2007 Aug 13.	Transporter-mediated absorption, secretion, and reabsorption of chemicals are increasingly recognized as important determinants in the biological activities of many xenobiotics. In recent years, the rapid progress in generating and characterizing mice with targeted deletion of transporters has greatly increased our knowledge of the functions of transporters in the pharmacokinetics/toxicokinetics of xenobiotics. In this introduction, we focus on functions of transporters learned from experiments on knockout mice as well as humans and rodents with natural mutations of these transporters. We limit our discussion to transporters that either directly transport xenobiotics or are important in biliary excretion or cellular defenses, namely multidrug resistance, multidrug resistance-associated proteins, breast cancer resistance protein, organic anion transporting polypeptides, organic anion transporters, organic cation transporters, nucleoside transporters, peptide transporters, bile acid transporters, cholesterol transporters, and phospholipid transporters, as well as metal transporters. Efflux transporters in intestine, liver, kidney, brain, testes, and placenta can efflux xenobiotics out of cells and serve as barriers against the entrance of xenobiotics into cells, whereas many xenobiotics enter the biological system via uptake transporters. The functional importance of a given transporter in each tissue depends on its substrate specificity, expression level, and the presence/absence of other transporters with overlapping substrate preferences. Nevertheless, a transporter may affect a tissue independent of its local expression by altering systemic metabolism. Further studies on the gene regulation and function of transporters, as well as the interrelationship between transporters and phase I/II xenobiotic-metabolizing enzymes, will provide a complete framework for developing novel strategies to protect us from xenobiotic insults.	●	●								-		C	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献ラン①抽出	文献ラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
161	ADME	Klamt, Andreas; Huniar, Uwe; Spycher, Simon; Keldenich, Jörg	COSMOmic: a mechanistic approach to the calculation of membrane-water partition coefficients and internal distributions within membranes and micelles	2008	J Phys Chem B. 2008 Sep 25;112(38):12148-57. doi: 10.1021/jp801736k. Epub 2008 Aug 28.	A new approach for the modeling of molecules in micellar systems and especially in biomembranes, COSMOmic, is presented, and its performance is validated on the example of the partitioning of molecules between water and biological membranes. Starting from quantum chemical calculations of the surfactant, solvent, and solute molecules, and being based on the COSMO-RS method for fluid-phase thermodynamic properties, COSMOmic is essentially free of additional adjustable parameters. The inclusion of an elastic energy correction into the COSMOmic model did not turn out to yield any significant improvement. The novel COSMOmic method allows for the efficient prediction of the distribution of molecules in micellar systems.	●	●								-		C	C
162	ADME	Kuczmarski, R. J.; Ogden, C. L.; Guo, S. S.; Grummer-Strawn, L. M.; Flegal, K. M.; Mei, Z.; Wei, R.; Curtin, L. R.; Roche, A. F.; Johnson, C. L.	2000 CDC growth charts for the United States: Methods and development	2002	Vital Health Stat. 11. 2002 May;(246):1-190.	OBJECTIVES: This report provides detailed information on how the 2000 Centers for Disease Control and Prevention (CDC) growth charts for the United States were developed, expanding upon the report that accompanied the initial release of the charts in 2000.METHODS: The growth charts were developed with data from five national health examination surveys and limited supplemental data. Smoothed percentile curves were developed in two stages. In the first stage, selected empirical percentiles were smoothed with a variety of parametric and nonparametric procedures. In the second stage, parameters were created to obtain the final curves, additional percentiles and z-scores. The revised charts were evaluated using statistical and graphical measures.RESULTS: The 1977 National Center for Health Statistics (NCHS) growth charts were revised for infants (birth to 36 months) and older children (2 to 20 years). New body mass index-for-age (BMI-for-age) charts were created. Use of national data improved the transition from the infant charts to those for older children. The evaluation of the charts found no large or systematic differences between the smoothed percentiles and the empirical data.CONCLUSION: The 2000 CDC growth charts were developed with improved data and statistical procedures. Health care providers now have an instrument for growth screening that better represents the racial-ethnic diversity and combination of breast- and formula-feeding in the United States. It is recommended that these charts replace the 1977 NCHS charts when assessing the size and growth patterns of infants, children, and adolescents.	●	●								-		C	C
163	ADME	Kullak-Ublick, G.,.A.; Hagenbuch, B.,.; Stieger, B.,.; Schteingart, C.,.D.; Hofmann, A.,.F.; Wolkoff, A.,.W.; Meier, P.,.J.	Molecular and functional characterization of an organic anion transporting polypeptide cloned from human liver	1995	Gastroenterology. 1995 Oct;109(4):1274-82. doi: 10.1016/0016-5085(95)90588-x.	Background & aims: Based on a recently cloned rat liver organic anion transporter, we attempted to clone the corresponding human liver organic anion transporting polypeptide.	●	●								-		C	C
164	ADME	Kummu, M.; Sieppi, E.; Koponen, J.; Laatio, L.; VÃ¤HÃ¤Kangas, K.; Kiviranta, H.; Rautio, A.; Myllynen, P.	Organic anion transporter 4 (OAT 4) modifies placental transfer of perfluorinated alkyl acids PFOS and PFOA in human placental ex vivo perfusion system	2015	Placenta. 2015 Oct;36(10):1185-91. doi: 10.1016/j.placenta.2015.07.119. Epub 2015 Aug 6.	INTRODUCTION: Perfluorinated alkyl acids (PFAAs) are widely used in industry and consumer products. Pregnant women are exposed to PFAAs and their presence in umbilical cord blood represents fetal exposure. Interestingly, PFAAs are substrates for organic anion transporters (OAT) of which OAT4 is expressed in human placenta.	●	●								-		B	B
165	ADME	Kusuhara, Hiroyuki; Sugiyama, Yuichi	In vitro-in vivo extrapolation of transporter-mediated clearance in the liver and kidney [Review]	2009	Drug Metab Pharmacokinet. 2009;24(1):37-52. doi: 10.2133/dmpk.24.37.	Transporters govern drug movement into and out of tissues, thereby playing an important role in drug disposition in plasma and to the site of action. The molecular cloning of such transporters has clarified the importance of members of the solute carrier family, such as OATP/SLCO, OCT/SLC22, OAT/SLC22, and MATE/SLC47, and the ATP-binding cassette transporters, such as P-glycoprotein/ABCB1, MRPs/ABCC, and BCRP/ABCG2. Elucidation of molecular characteristics of transporters has allowed the identification of transporters as mechanisms for drug-drug interactions, and of interindividual differences in drug dispositions and responses. Cumulative studies have highlighted the cooperative roles of uptake transporters and metabolic enzymes/efflux transporters. In this way, the concept of a rate-limiting process in hepatic/renal elimination across epithelial cells has developed. This review illustrates the concept of the rate-limiting step in the hepatic elimination mediated by transporters, and describes the prediction of the in vivo pharmacokinetics of drugs whose disposition is determined by transporters, based on in vitro experiments using pravastatin as an example. This review also illustrates the transporters regulating the peripheral drug concentrations.	●	●								-		C	C
166	ADME	Launay-Vacher, Vincent; Izzedine, Hassane; Karie, Svetlana; Hulot, Jean Sébastien; Baumelou, Alain; Deray, Gilbert	Renal tubular drug transporters	2006	Nephron Physiol. 2006;103(3):p97-106. doi: 10.1159/000092212. Epub 2006 Mar 22.	The kidney plays an important role in the elimination of numerous hydrophilic xenobiotics, including drugs, toxins, and endogenous compounds. It has developed high-capacity transport systems to prevent urinary loss of filtered nutrients, as well as electrolytes, and simultaneously to facilitate tubular secretion of a wide range of organic ions. Transport systems for organic anions and cations are primarily involved in the secretion of drugs in renal tubules. The identification and characterization of organic anion and cation transporters have been progressing at the molecular level. To date, many members of the organic anion transporter, organic cation transporter, and organic anion-transporting polypeptide families have been found to mediate the transport of diverse organic ions. It has also been suggested that ATP-dependent primary active transporters such as MDR1/P-glycoprotein and the multidrug resistance-associated protein family function as efflux pumps of renal tubular cells for more hydrophobic molecules and anionic conjugates. Tubular reabsorption of peptide-like drugs such as beta-lactam antibiotics across the brush-border membranes appears to be mediated by two distinct H+/peptide cotransporters: PEPT1 and PEPT2. Renal disposition of drugs occurs through interaction with these diverse secretory and absorptive transporters in renal tubules. Studies of the functional characteristics, such as substrate specificity and transport mechanisms, and of the localization of drug transporters could provide information regarding the cellular network involved in renal handling of drugs. Detailed information concerning molecular and cellular aspects of drug transporters expressed in the kidney has facilitated studies of the mechanisms underlying renal disposition as well as transporter-mediated drug interactions.	●	●								-		C	C
167	ADME	Lehmann, Geniece M; Verner, Marc-André; Luukinen, Bryan; Henning, Cara; Assimon, Sue Anne; LaKind, Judy S; McLanahan, Eva D; Phillips, Linda J; Davis, Matthew H; Powers, Christina M; Hines, Erin P; Haddad, Sami; Longnecker, Matthew P; Poulsen, Michael T; Farrer, David G; Marchitti, Satori A; Tan, Yu-Mei; Swartout, Jeffrey C; Sagiv, Sharon K; Welsh, Clement; Campbell, Jerry L Jr; Foster, Warren G; Yang, Raymond S H; Fenton, Suzanne E; Tornero-Velez, Rogelio; Francis, Bettina M; Barnett, John B; El-Masri, Hisham A; Simmons, Jane Ellen	Improving the risk assessment of lipophilic persistent environmental chemicals in breast milk [Review]	2014	Crit Rev Toxicol. 2014 Aug;44(7):600-17. doi: 10.3109/10408444.2014.926306.	Lipophilic persistent environmental chemicals (LPECs) have the potential to accumulate within a woman's body lipids over the course of many years prior to pregnancy, to partition into human milk, and to transfer to infants upon breastfeeding. As a result of this accumulation and partitioning, a breastfeeding infant's intake of these LPECs may be much greater than his/her mother's average daily exposure. Because the developmental period sets the stage for lifelong health, it is important to be able to accurately assess chemical exposures in early life. In many cases, current human health risk assessment methods do not account for differences between maternal and infant exposures to LPECs or for lifestage-specific effects of exposure to these chemicals. Because of their persistence and accumulation in body lipids and partitioning into breast milk, LPECs present unique challenges for each component of the human health risk assessment process, including hazard identification, dose-response assessment, and exposure assessment. Specific biological modeling approaches are available to support both dose-response and exposure assessment for lactational exposures to LPECs. Yet, lack of data limits the application of these approaches. The goal of this review is to outline the available approaches and to identify key issues that, if addressed, could improve efforts to apply these approaches to risk assessment of lactational exposure to these chemicals.	●	●								-		C	C
168	ADME	Li, K.; Li, C.; Yu, N. Y.; Juhasz, A. L.; Cui, X. Y.; Ma, L. Q.	In vivo bioavailability and in vitro bioaccessibility of perfluorooctanoic acid (PFOA) in food matrices: correlation analysis and method development	2015	Environ Sci Technol. 2015 Jan 6;49(1):150-8. doi: 10.1021/es505075z.	Food is a major source of human exposure to perfluorooctanoic acid (PFOA), however, PFOA bioavailability in food has not been studied. An in vivo mouse model and three in vitro methods (unified BARGE method, UBM; physiologically based extraction test, PBET; and in vitro digestion method, IVD) were used to determine the relative bioavailability and bioaccessibility of PFOA in the presence of 17 foods. PFOA was mixed with foods of different nutritional compositions and fed to mice over a 7-d period. PFOA relative bioavailability was determined by comparing PFOA accumulation in the liver following PFOA exposure via food to that in water. PFOA bioavailability relative to water ranged from 4.3 ± 0.8 to 69 ± 0.119 and was negatively correlated with lipid content (r = 0.76). This was possibly due to competitive sorption of free fatty acids with PFOA onto transporters on intestine epithelial cells. Besides, cations in the gastrointestinal tract, such as Ca(2+) and Mg(2+), are capable of complexing PFOA and partitioning to the lipid phase. On the other hand, when assessed using in vitro assays, PFOA bioaccessibility varied with methods, being 8.7-73% (UBM), 9.8-99% (PBET), and 21-114% (IVD). PFOA bioaccessibility was negatively correlated with lipid content when assessed using UBM (r = 0.82); however, a poor correlation with food composition was observed for PBET and IVD (r = 0.01-0.50). When in vivo and in vitro data were compared, a strong correlation was observed for UBM (r = 0.79), but poor relationships were observed for PBET and IVD (r = 0.11-0.22). This was probably because the higher lipolysis ability and presence of Ca(2+) and Mg(2+) in the gastrointestinal fluid of UBM resulted in a lower potential to form stable micelles compared to PBET and IVD. These results indicated that PFOA relative bioavailability was mainly affected by lipid content in foods, and UBM has the potential to determine PFOA bioaccessibility in food samples.	●	●								-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報抽出対象	文献ランク①	文献ランク②
169	ADME	Li, K.; Sun, J.; Yang, J.; Roberts, S. M.; Zhang, X.; Cui, X.; Wei, S.; Ma, L. Q.	Molecular Mechanisms of Perfluorooctanoate-Induced Hepatocyte Apoptosis in Mice Using Proteomic Techniques	2017	Environ Sci Technol. 2017 Oct 3;51(19):11380-11389. doi: 10.1021/acs.est.7b02690. Epub 2017 Sep 21.	The stability of perfluorooctanoate (PFOA) coupled with its wide use cause serious concerns regarding its potential risk to human health. The molecular mechanisms of PFOA-induced hepatotoxicity relevant to human health was investigated using both in vivo (mouse model) and in vitro (human hepatocyte cells, HL-7702) techniques. Both male and female Balb/c mice were administered PFOA at 0.05, 0.5, or 2.5 mg/kg-d for 28-d, with serum PFOA concentrations after exposure being found at environmentally relevant levels. Liver samples were examined for histology and proteomic change using iTRAQ and Western Blotting, showing dose-dependent hepatocyte apoptosis and peroxisome proliferation. At high doses, genotoxicity resulting from ROS hypergeneration was due to suppression of Complex I subunits in the electron transport chain and activation of PPARα in both genders. However, at 0.05 mg/kg-d, Complex I suppression occurred only in females, making them more sensitive to PFOA-induced apoptosis. In vitro assays using HL-7702 cells confirmed that apoptosis was also induced through a similar mechanism. The dose/gender-dependent toxicity mechanisms help to explain some epidemiological phenomena, i.e., liver cancer is not often associated with PFOA exposure in professional workers. Our results demonstrated that a proteomic approach is a robust tool to explore molecular mechanisms of toxic chemicals at environmentally relevant levels.	●	●								-		-	B
170	ADME	Li, Y, ing; Mucs, D, aniel; Scott, K, ristin; Lindh, C, hristian; Tallving, P, ia; Fletcher, T, ony; Jakobsson, K, ristina.	Half-lives of PFOS, PFHxS and PFOA after end of exposure to contaminated drinking water	2018	Occup Environ Med. 2018 Jan;75(1):46-51. doi: 10.1136/oemed-2017-104651. Epub 2017 Nov 13.	Background: Municipal drinking water contaminated with perfluorinated alkyl acids had been distributed to one-third of households in Ronneby, Sweden. The source was firefighting foam used in a nearby airfield since the mid-1980s. Clean water was provided from 16 December 2013. Objective: To determine the rates of decline in serum perfluorohexane sulfonate (PFHxS), perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA), and their corresponding half-lives. Methods: Up to seven blood samples were collected between June 2014 and September 2016 from 106 participants (age 4-84 years, 53% female). Results: Median initial serum concentrations were PFHxS, 277 ng/mL (range 12-1660); PFOS, 345 ng/mL (range 24-1500); and PFOA, 18 ng/mL (range 2.4-92). The covariate-adjusted average rates of decrease in serum were PFHxS, 13% per year (95% CI 12% to 15%); PFOS, 20% per year (95% CI 19% to 22%); and PFOA, 26% per year (95% CI 24% to 28%). The observed data are consistent with a first-order elimination model. The mean estimated half-life was 5.3 years (95% CI 4.6 to 6.0) for PFHxS, 3.4 years (95% CI 3.1 to 3.7) for PFOS and 2.7 years (95% CI 2.5 to 2.9) for PFOA. The interindividual variation of half-life was around threefold when comparing the 5th and 95th percentiles. There was a marked sex difference with more rapid elimination in women for PFHxS and PFOS, but only marginally for PFOA. Conclusions: The estimated half-life for PFHxS was considerably longer than for PFOS and PFOA. For PFHxS and PFOS, the average half-life is shorter than the previously published estimates. For PFOA the half-life is in line with the range of published estimates.	●									-	1	A	A
171	ADME	Liu, Y.; Cao, Z.; Zong, W.; Liu, R.	Interaction rule and mechanism of perfluoroalkyl sulfonates containing different carbon chains with human serum albumin	2017	RSC Advances. 7(40):24781-24788, doi: 10.1039/C7RA02963B	In this study, the toxic mechanism and effects of perfluorooctane sulfonate (PFOS), perfluorohexane sulfonate (PFHS), and perfluorobutane sulfonate (PFBS) were investigated via spectroscopy, molecular modeling, and calorimetry techniques. Results showed that all three perfluoroalkyl sulfonates (PFASs) bound to human serum albumin (HSA) mainly through electrostatic forces and hydrogen bonds. The backbone and secondary structure of HSA did not significantly change after exposure to PFASs. It may be proposed that the binding changed the local structure around the active site and affected the esterase activity of HSA. Compared with the control group, the inhibited esterase activity of HSA decreased to 28.6%, 43.2%, and 0.544 under the exposure of PFOS, PFHS, and PFBS at 1.3 x 10(-4) mol L-1, respectively. The ITC result reflected that the binding ability increased after lengthening of the carbon chain, which also explained the decreased esterase activity with the increased lengthening of carbon chain. The fluorescence spectra also indicated that the influence on the microenvironment of HSA decreased with the shortening of the carbon chain. This study provided evidence regarding the interaction mechanism and toxicity of PFASs towards HSA in vitro.	●									-		B	B
172	ADME	Loccisano, A. E.; Campbell, J. L., Jr; Butenhoff, J. L.; Andersen, M. E.; Clewell, H. J., III	Comparison and evaluation of pharmacokinetics of PFOA and PFOS in the adult rat using a physiologically based pharmacokinetic model	2012	Reprod Toxicol. 2012 Jul;33(4):452-467. doi: 10.1016	Perfluoroalkyl acid carboxylates and sulfonates (PFAAs) have many consumer and industrial applications. The persistence and widespread distribution of PFAAs have brought them under intense scrutiny. Limited PK data for PFAAs is available for humans; however, toxicological and pharmacokinetic data exist for rats, which can be useful for cross-species extrapolation. In this work, PBPK models were developed for adult male and female rats to describe the pharmacokinetics of PFOA and PFOS. The models contain a description of saturable renal resorption, free fraction of chemical in plasma, and saturable binding in liver. Both male and female rat models for each chemical were consistent with available PK data resulting from IV, oral, and dietary dosing regimens. Predicted plasma concentration curves followed trends observed in experimental data, and model predictions were within a factor of two of experimental values. PFOA and PFOS rat model output is sensitive to parameters governing renal resorption, indicating that renal resorption is responsible for the long-half life. These models, along with the PFAA gestation and lactation models published in this issue, will help address concerns about possible health effects due to PFAA exposure in the fetus and neonate and will be useful in comparing PK across life stages.	●	●		●	●	●				-		A	B
173	ADME	Loccisano, A. E.; Campbell, J. L.; Butenhoff, J. L.; Andersen, M. E.; Clewell, H. J.	Evaluation of placental and lactational pharmacokinetics of PFOA and PFOS in the pregnant, lactating, fetal and neonatal rat using a physiologically based pharmacokinetic model	2012	Reprod Toxicol. 2012 Jul;33(4):468-490. doi: 10.1016	Perfluoroalkyl carboxylates and sulfonates (PFAAs) have many consumer and industrial applications. Developmental toxicity studies in animals have raised concern about potential developmental effects of PFOA and PFOS in humans. We have developed PBPK models for PFAAs in the rat to help define a relationship between external dose, internal tissue concentrations, and observed adverse effects, and to understand how physiological changes that occur during gestation and lactation affect tissue distribution of PFAAs in the mother, fetus, and neonate. The models developed here expand upon a PBPK model for PFAAs in the adult female rat, and are consistent with available PK data. These models, along with the adult rat PFAA models, published in the companion paper, will help address concerns about possible health effects due to PFAA exposure in the fetus and neonate and will be useful in comparing PK across life stages.	●	●		●	●	●				-		A	B
174	ADME	Lou, Inchio; Wambaugh, John F; Lau, Christopher; Hanson, Roger G; Lindstrom, Andrew B; Strynar, Mark J; Zehr, R Dan; Setzer, R Woodrow; Barton, Hugh A	Modeling single and repeated dose pharmacokinetics of PFOA in mice	2009	Toxicol Sci. 2009 Feb;107(2):331-41. doi: 10.1093/toxsci/kfn234. Epub 2008 Nov 12.	Perfluorooctanoic acid (PFOA) displays complicated pharmacokinetics in that serum concentrations indicate long half-lives despite which steady state appears to be achieved rapidly. In this study, serum and tissue concentration time-courses were obtained for male and female CD1 mice after single, oral doses of 1 and 10 mg/kg of PFOA. When using one- and two-compartment models, the pharmacokinetics for these two dosages are not consistent with serum time-course data from female CD1 mice administered 60 mg/kg, or with serum concentrations following repeated daily doses of 20 mg/kg PFOA. Some consistency between dose regimens could be achieved using the saturable resorption model of Andersen et al. In this model PFOA is cleared from the serum into a filtrate compartment from which it is either excreted or resorbed into the serum by a process presumed transporter mediated with a Michaelis-Menten form. Maximum likelihood estimation found a transport maximum of T(m) = 860.9 (1298.3) mg/l/h and half-maximum concentration of K(T) = 0.0015 (0.0022) mg/l where the estimated standard errors (in parentheses) indicated large uncertainty. The estimated rate of flow into and out of the filtrate compartment, 0.6830 (1.0131) l/h was too large to be consistent with a biological interpretation. For these model parameters a single dose greater than 40 mg/kg, or a daily dose in excess of 5 mg/kg were necessary to observe nonlinear pharmacokinetics for PFOA in female CD1 mice. These data and modeling analyses more fully characterize PFOA in mice for purposes of estimating internal exposure for use in risk assessment.	●	●		●		●			●	-		B	B
175	ADME	Mamsen, L. S.; Björvang, R. D.; Mucs, D.; Vinnars, M. T.; Papadogiannakis, N.; Lindh, C. H.; Andersen, C. Y.; Damdimopoulou, P.	Concentrations of perfluoroalkyl substances (PFASs) in human embryonic and fetal organs from first, second, and third trimester pregnancies	2019	Environ Int. 2019 Mar;124:482-492. doi: 10.1016/j.envint.2019.01.010. Epub 2019 Jan 24.	BACKGROUND: The persistent environmental contaminants perfluoroalkyl substances (PFASs) have gained attention due to their potential adverse health effects, in particular following early life exposure. Information on human fetal exposure to PFASs is currently limited to one report on first trimester samples. There is no data available on PFAS concentrations in fetal organs throughout all three trimesters of pregnancy.METHODS: We measured the concentrations of perfluorooctanesulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnA), and perfluorohexane sulfonic acid (PFHxS) in human embryos and fetuses with corresponding placentas and maternal serum samples derived from elective pregnancy terminations and cases of intrauterine fetal death. A total of 78 embryos and fetuses aged 15523 gestational weeks were included and a total of 225 fetal organs covering liver, lung, heart, central nervous system (CNS), and adipose tissue were analyzed, together with 71 placentas and 63 maternal serum samples. PFAS concentrations were assayed by liquid chromatography/triple quadrupole mass spectrometry.RESULTS: All evaluated PFASs were detected and quantified in maternal sera, placentas and embryos/fetuses. In maternal serum samples, PFOS was detected in highest concentrations, followed by PFOA > PFNA > PFDA = PFUnA = PFHxS. Similarly, PFOS was detected in highest concentrations in embryo/fetal tissues, followed by PFOA > PFNA = PFDA = PFUnA. PFHxS was detected in very few fetuses. In general, PFAS concentrations in embryo/fetal tissue (ng/g) were lower than maternal serum (ng/ml) but similar to placenta concentrations. The total PFAS burden (i.e. the sum of all PFASs) was highest in lung tissue in first trimester samples and in liver in second and third trimester samples. The burden was lowest in CNS samples irrespective of fetal age. The placenta:maternal serum ratios of PFOS, PFOA and PFNA increased across gestation suggesting bioaccumulation in the placenta. Further, we observed that the ratios were higher in pregnancies with male fetuses compared to female fetuses.CONCLUSIONS: Human fetuses were intrinsically exposed to a mixture of PFASs throughout gestation. The compounds were detected in all analyzed tissues, suggesting that PFASs reach and may affect many types of organs. Collectively, our results demonstrate that PFASs pass the placenta and deposit to embryo and fetal tissues, calling for risk assessment of gestational exposures.	●	●								-	1	A	A

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ラン①抽出	文献ラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
176	ADME	Mamsen, L. S.; Jönsson, B. A. G.; Lindh, C. H.; Olesen, R. H.; Larsen, A.; Ernst, E.; Kelsey, T. W.; Andersen, C. Y.	Concentration of perfluorinated compounds and cotinine in human foetal organs, placenta, and maternal plasma	2017	Sci Total Environ. 2017 Oct 15;596-597:97-105. doi: 10.1016/j.scitotenv.2017.04.058.	BACKGROUND: Perfluoroalkyl substances (PFASs) are bio-accumulative pollutants, and prenatal exposure to PFASs is believed to impact human foetal development and may have long-term adverse health effects later in life. Additionally, maternal cigarette smoking may be associated with PFAS levels. Foetal exposure has previously been estimated from umbilical cord plasma, but the actual concentration in foetal organs has never been measured.OBJECTIVES: The concentrations of 5 PFASs and cotinine - the primary metabolite of nicotine - were measured in human foetuses, placentas, and maternal plasma to evaluate to what extent these compounds were transferred from mother to foetus and to determine if the PFAS concentrations were associated with maternal cigarette smoking.METHODS: Thirty-nine Danish women who underwent legal termination of pregnancy before gestational week 12 were included; 24 maternal blood samples were obtained together with 34 placental samples and 108 foetal organs. PFASs and cotinine were assayed by liquid chromatography/triple quadrupole mass spectrometry.RESULTS: In foetal organs, the average concentrations of perfluorooctanesulphonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluoroundecanoic acid (PFUnDa), and perfluorodecanoic acid (PFDA) were 0.6ng/g, 0.2ng/g, 0.1ng/g, 0.1ng/g, and 0.1ng/g, respectively. A significant positive correlation was found between the exposure duration, defined as foetal age, and foetal to maternal ratio for all five PFASs and cotinine. Smokers presented 99ng/g cotinine in plasma, 108ng/g in placenta, and 61ng/g in foetal organs. No correlation between the maternal cotinine concentrations and PFAS concentrations was found.CONCLUSIONS: PFASs were transferred from mother to foetus, however, with different efficiencies. The concentrations of PFOS, PFOA, PFNA, PFUnDA, and PFDA in foetal organs were much lower than the maternal concentrations. Furthermore, a significant correlation between the exposure duration and all of the evaluated PFASs was found. The health-compromising concentrations of these substances during foetal development are unknown.	●	●								-		B	A
177	ADME	Manzano-Salgado, Cyntia B; Casas, Maribel; Lopez-Espinosa, Maria-Jose; Ballester, Ferran; Basterrechea, Mikel; Grimalt, Joan O; Jiménez, Ana-María; Kraus, Thomas; Schettgen, Thomas; Sunyer, Jordi; Vrijheid, Martine	Transfer of perfluoroalkyl substances from mother to fetus in a Spanish birth cohort	2015	Environ Res. 2015 Oct;142:471-8. doi: 10.1016/j.envres.2015.07.020. Epub 2015 Aug 7.	INTRODUCTION: Prenatal exposure to perfluoroalkyl substances (PFAS) might affect child health; thus estimating PFAS fetal burden is relevant. PFAS fetal burden is best estimated in cord samples; previous studies have used either maternal plasma or serum during pregnancy as proxy, but their validity is not clear. We aimed to evaluate PFAS transfer between mother and fetus and determine its predictors in a Spanish birth cohort. METHODS: We measured perfluorobutane sulfonate (PFBS), perfluorohexane sulfonate (PFHxS), perfluorooctane sulfonate (PFOS), perfluorooctanoate (PFOA), and perfluorononanoate (PFNA) in maternal blood and cord serum from 66 mother-child pairs. We used Spearman's rank coefficients to correlate PFAS concentrations in first trimester maternal plasma and serum, with cord serum samples. We assessed PFAS placental transfer by calculating maternal to cord ratios and examined their association with maternal socio-demographic characteristics and child sex using linear regression models. RESULTS: Median concentrations of PFAS (ng/mL) of PFHxS, PFOS, PFOA, and PFNA in maternal plasma (0.79, 6.18, 2.85 and 0.84, respectively) and serum (0.84, 6.99, 2.97 and 0.85) were higher than in cord serum (0.40, 1.86, 1.90 and 0.32). PFBS was not detected. Positive Spearman's correlations (p-values<0.001) were found between maternal plasma and serum ($\rho \geq 0.80$), maternal plasma and cord ($\rho \geq 0.66$), and maternal serum and cord samples ($\rho \geq 0.67$). Maternal plasma to cord ratios were above 1 (PFHxS: 2.35 [95%CI: 2.05, 2.70], PFOS: 3.33 [3.05, 3.62], PFOA: 1.37 [1.27, 1.48], PFNA: 2.39 [2.18, 2.63]); maternal serum to cord ratios were similar. Maternal to cord ratios decreased with maternal age, but not with other socio-demographic factors. CONCLUSIONS: Our results suggest that PFAS fetal body burden can be assessed using as proxy maternal plasma or serum collected early in pregnancy. Maternal age might influence PFAS placental transfer.	●	●		●						-		B	A
178	ADME	Midasch, O; Drexler, H; Hart, N; Beckmann, M W; Angerer, J	Transplacental exposure of neonates to perfluorooctanesulfonate and perfluorooctanoate: a pilot study	2007	Int Arch Occup Environ Health. 2007 Jul;80(7):643-8. doi: 10.1007/s00420-006-0165-9. Epub 2007 Jan 12.	OBJECTIVES: Perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) can be released of perfluorinated compounds by biotic and/or metabolic decomposition. Due to their ubiquitous occurrence, persistence and bioaccumulative properties they can be found in blood of the general population all over the world. In animal studies PFOS and PFOA provoked cancer and showed developmental toxic potential besides other adverse health effects. On the basis of the comparison of maternal and umbilical cord plasma sample pairs we wanted to examine whether infants are exposed to PFOS and PFOA via their mothers' blood. METHODS: We determined PFOS and PFOA in 11 plasma samples of mothers and the 11 corresponding cord plasma samples of neonates. An analytical method based on plasma protein precipitation followed by HPLC with MS/MS-detection was employed. As internal standards we used 1,2,3,4-(13)C(4)-PFOS and 1,2-(13)C(2)-PFOA. RESULTS: We found PFOS and PFOA in every plasma sample analysed. In maternal plasma samples PFOS concentrations were consistently higher compared to those of the related cord plasma samples (median: 13.0 microg/l vs. 7.3 microg/l). In the case of PFOA we observed only minor differences between PFOA concentrations within the analysed sample pairs (median: 2.6 microg/l vs. 3.4 microg/l for maternal and cord plasma samples, respectively). DISCUSSION: For both substances a crossing of the placental barrier could be shown. For PFOS we observed a decrease from maternal to cord plasma concentrations by a factor of 0.41-0.80. To the contrary, PFOA crosses the placental barrier obviously unhindered. These findings show that neonates are exposed to PFOS and PFOA via their mothers' blood. Given the current situation that only little is known about the consequences of PFOS and PFOA exposure in the early state of development of humans and the fact that in animal studies both substances showed developmental toxic effects further research regarding human health effects is indispensable.	●	●		●	●	●				-		B	B
179	ADME	Mordenti, J.,.; Chen, S.,. A.; Moore, J.,. A.; Ferraiolo, B.,. L.; Green, J.,. D.	Interspecies scaling of clearance and volume of distribution data for five therapeutic proteins	1991	Pharm Res. 1991 Nov;8(11):1351-9. doi: 10.1023/a:1015836720294.	The clearance and volume of distribution of five human proteins (recombinant CD4, CD4 immunoglobulin G, growth hormone, tissue-plasminogen activator, and relaxin) in humans and laboratory animals were analyzed as a function of body weight using allometric scaling techniques. These proteins cover a 16-fold range of molecular weight (6 to 98 kD), are produced by recombinant or synthetic methods, and may be cleared by different mechanisms. The analyses revealed that the clearance and volume data for each protein were satisfactorily described by an allometric equation (Y = a Wb). The allometric exponent (b) for clearance (ml/min) ranged from 0.65 to 0.84, the allometric exponent for the initial volume of distribution (ml) ranged from 0.83 to 1.05, and the allometric exponent for the volume of distribution at steady state (ml) ranged from 0.84 to 1.02. Exponent values from 0.6 to 0.8 for clearance and 0.8 to 1 for volumes are frequently cited for small molecules and are expected based on empirical interspecies relationships. When the preclinical data were analyzed separately, the preclinical allometric relationships were usually predictive of the human results. These findings indicate that the clearance and volume of distribution of select biomacromolecules follow well-defined, size-related physiologic relationships, and preclinical pharmacokinetic studies provide reasonable estimates of human disposition. Employing this methodology during the early phases of drug development may provide a more rational basis for dose selection in the clinical environment.	●	●								-		C	D
180	ADME	Nakagawa, H.; Hirata, T.; Terada, T.; Jutabha, P.; Miura, D.; Harada, K. H.; Inoue, K.; Anzai, N.; Endou, H.; Inui, K.; Kanai, Y.; Koizumi, A.	Roles of organic anion transporters in the renal excretion of perfluorooctanoic acid	2008	Basic Clin Pharmacol Toxicol. 2008 Jul;103(1):1-8. doi: 10.1111/j.1742-7843.2007.00155.x. Epub 2008 Jul 1.	Perfluorooctanoic acid, an environmental contaminant, is found in both wild animals and human beings. There are large species and sex differences in the renal excretion of perfluorooctanoic acid. In the present study, we aimed to characterize organic anion transporters 44564 (OAT1-3) in human beings and rats to investigate whether the species differences in the elimination kinetics of perfluorooctanoic acid from the kidneys can be attributed to differences in the affinities of these transporters for perfluorooctanoic acid. We used human (h) and rat (r) OAT transient expression cell systems and measured the [(14)C] perfluorooctanoic acid transport activities. Both human and rat OAT1 and OAT3 mediated perfluorooctanoic acid transport to similar degrees. Specifically, the kinetic parameters, K(m), were 48 +/- 6.4 microM for h OAT1; 51 +/- 12 microM for rOAT1; 49.1 +/- 21.4 microM for hOAT3 and 80.2 +/- 17.8 microM for rOAT3, respectively. These data indicate that both human and rat OAT1 and OAT3 have high affinities for perfluorooctanoic acid and that the species differences in its renal elimination are not attributable to affinity differences in these OATs between human beings and rats. In contrast, neither hOAT2 nor rOAT2 transported perfluorooctanoic acid. In conclusion, OAT1 and OAT3 mediated perfluorooctanoic acid transport in vitro, suggesting that these transporters also transport perfluorooctanoic acid through the basolateral membrane of proximal tubular cells in vivo in both human beings and rats. Neither human nor rat OAT2 mediated perfluorooctanoic acid transport. Collectively, the difference between the perfluorooctanoic acid half-lives in human beings and rats is not likely to be attributable to differences in the affinities of these transporters for perfluorooctanoic acid.	●	●		●						-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献クラン①A	文献クラン②B
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
181	ADME	Nakagawa, H.; Terada, T.; Harada, K. H.; Hitomi, T.; Inoue, K.; Inui, K.; Koizumi, A.	Human organic anion transporter hOAT4 is a transporter of perfluorooctanoic acid	2009	Basic Clin Pharmacol Toxicol. 2009 Aug;105(2):136-8. doi: 10.1111/j.1742-7843.2009.00409.x. Epub 2009 Apr 3.	Perfluorooctanoic acid is a class of synthetic fluorochemicals used in a variety of applications such as processing aids for fluoropolymer production, surfactants and water-repellent coatings [1, 2]. It poses special public health concerns due to its long-term persistence and bioaccumulation in the environment, including humans [3-5]. There have been a number of reports regarding the health effects of perfluorooctanoic acid. It was found to be a carcinogen for rodents [6] while it is not genotoxic in umu test [7]. Furthermore, a developmental toxicity study of perfluorooctanoic acid in mice revealed early total loss and delays in general growth and development [8]. Species and sex differences have been reported for the toxicokinetics of perfluorooctanoic acid. Human serum elimination half-life of perfluorooctanoic acid is reported to be 3.8 years [9]. However, its serum elimination half-lives are much shorter in male Wistar rats (5.7 days) [10] suggesting large differences in perfluorooctanoic acid elimination kinetics among species. In clear contrast to rats, renal clearance of perfluorooctanoic acid in humans is negligible [11]. Although several organic anion transporters (OATs) are found to mediate transport of perfluorooctanoic acid in rats and humans, there were no kinetically significant difference in their activities [12, 13]. Assuming that perfluorooctanoic acid transport from serum to tubular epithelial cells would be expected to occur in similar manners in both species, it is reasonable to predict a critical role for the re-absorption process as a determinant for the large species differences observed in the renal excretion of perfluorooctanoic acid. OAT4 (SLC22A11), a transporter that is only expressed in humans, is an apical type isoform in proximal tubules and mediates the re-absorption of organic anions [14]. Therefore, it may contribute to the long half-life of perfluorooctanoic acid in humans. In the present study, we aimed to characterize the perfluorooctanoic acid transport activity of human OAT4.	●	●		●						-		A	B
182	ADME	Needham, L. L.; Grandjean, P.; Heinzow, B.; Jørgensen, P. J.; Nielsen, F.; Patterson, D. G.; Sjödin, A.; Turner, W. E.; Weihe, P.	Partition of environmental chemicals between maternal and fetal blood and tissues	2011	Environ Sci Technol. 2011 Feb 1;45(3):1121-6. doi: 10.1021/es1019614. Epub 2010 Dec 17.	Passage of environmental chemicals across the placenta has important toxicological consequences, as well as for choosing samples for analysis and for interpreting the results. To obtain systematic data, we collected in 2000 maternal and cord blood, cord tissue, placenta, and milk in connection with births in the Faroe Islands, where exposures to marine contaminants is increased. In 15 sample sets, we measured a total of 87 environmental chemicals, almost all of which were detected both in maternal and fetal tissues. The maternal serum lipid-based concentrations of organohalogen compounds averaged 1.7 times those of cord serum, 2.8 times those of cord tissue and placenta, and 0.7 those of milk. For organohalogen compounds detectable in all matrices, a high degree of correlation between concentrations in maternal serum and the other tissues investigated was generally observed (r(2) > 0.5). Greater degree of chlorination resulted in lower transfer from maternal serum into milk. Concentrations of pentachlorbenzene, γ-hexachlorocyclohexane, and several polychlorinated biphenyl congeners with low chlorination were higher in fetal samples and showed poor correlation with maternal levels. Perfluorinated compounds occurred in lower concentrations in cord serum than in maternal serum. Cadmium, lead, mercury, and selenium were all detected in fetal samples, but only mercury showed close correlations among concentrations in different matrices. Although the environmental chemicals examined pass through the placenta and are excreted into milk, partitions between maternal and fetal samples are not uniform.	●	●		●	●					-		B	A
183	ADME	Nilsson, H; K?rrman, A; Rotander, A; van Bavel, B; Lindstr?m, G; Westberg, H.	Biotransformation of fluorotelomer compound to perfluorocarboxylates in humans	2013	Environ Int. 2013 Jan;51:8-12. doi: 10.1016/j.envint.2012.09.001. Epub 2012 Nov 6.	Levels of perfluorocarboxylates (PFCAs) in biological compartments have been known for some time but their transport routes and distribution patterns are not properly elucidated. The opinions diverge whether the exposure of the general population occurs indirect through precursors or direct via PFCAs. Previous results showed that ski wax technicians are exposed to levels up to 92 000 ng/m(3) of 8:2 fluorotelomer alcohol (FTOH) via air and have elevated blood levels of PFCAs. Blood samples were collected in 2007-2011 and analyzed for C(4)-C(18) PFCAs, 6:2, 8:2 and 10:2 unsaturated fluorotelomer acids (FTUCAs) and 3:3, 5:3 and 7:3 fluorotelomer acids (FTCAs) using UPLC-MS/MS. Perfluorooctanoic acid (PFOA) was detected in levels ranging from 1.90 to 628 ng/mL whole blood (wb). Metabolic intermediates 5:3 and 7:3 FTCA were detected in all samples at levels up to 6.1 and 3.9 ng/mL wb. 6:2, 8:2 and 10:2 FTUCAs showed maximum levels of 0.07, 0.64 and 0.11 ng/mL wb. Also, for the first time levels of PFHxDA and PFOcDA were detected in the human blood at mean concentrations up to 4.22 ng/mL wb and 4.25 ng/mL wb respectively. The aim of this study was to determine concentrations of PFCAs and FTOH metabolites in blood from ski wax technicians.	●	●								-		B	B
184	ADME	Noker, PE; Gorman, G.	A Pharmacokinetic Study of Potassium Perfluorooctanesulfonate in the Cynomolgus Monkey	2003	U.S. EPA docket AR-226-1356	No abstract available	●	●		●						USEPA Public Docket AR226-1356で検索したが入手できず		D	D
185	ADME	O'Malley, K. D.; Ebbins, K. L.	Repeat application 28 day percutaneous absorption study with T-2618CoC in albino rabbits	1981	USEPA Administrative Record 226-0446	No abstract available	●	●							●	USEPA Administrative Record 226-0446で検索したが入手できず		D	D
186	ADME	Olsen, G.,.; Ehresman, D.,.; Froehlich, J.; Burris, J.,.; Butenhoff, J.,.	Evaluation of the Half-life (T1/2) of Elimination of Perfluorooctanesulfonate (PFOS), Perfluorohexanesulfonate (PFHS) and Perfluorooctanoate (PFOA) from Human Serum	2005	St. Paul, MN: 3M Company.	PFOS is well-absorbed orally and very slowly eliminated from the body, and these combined properties can result in the accumulation of PFOS body burden from various sources and pathways of exposure. Elimination half-lives after i.v. injection in rats and monkeys are currently estimated to be in the range of 100 days to 150 days. Enterohepatic circulation likely plays a predominant role in the long elimination half-life of PFOS. Serum elimination half-lives for PFHS in cynomolgus monkeys have been estimated at approximately two-thirds less than PFOS, and limited data in rats also suggests a shorter elimination. Marked sex and species differences occur in the elimination of PFOA. Urine is the primary route of excretion for PFOA. The elimination half-life in male rats is 44657 days and 44596 hours in females, and is approximately 21 and 30 days in male and female monkeys, respectively. Sex hormones may modulate differential expression of organic anion transporters involved in the urine elimination of PFOA in rats.	●	●								-		B	B
187	ADME	Olsen, G.,.W.	Identification of Fluorochemicals in Human Tissue	2001	U.S. Environmental Protection Agency Administrative Record 226-1030a022	No abstract available	●									USEPA Administrative Record226-1030a022で検索したが入手できず		D	D
188	ADME	Olsen, G. W.; Hansen, K. J.; Stevenson, L. A.; Burris, J. M.; Mandel, J. H.	Human donor liver and serum concentrations of perfluorooctanesulfonate and other perfluorochemicals	2003	Environ Sci Technol. 2003 Mar 1;37(5):888-91. doi: 10.1021/es020955c.	Perfluorooctanesulfonate (PFOS, CaF17SO3-) has been identified in the serum of nonoccupationally exposed humans and in serum and liver tissue in wildlife. The purpose of this investigation was to determine whether PFOS liver concentrations in humans are comparable to the approximate 30 ng/mL average serum concentrations reported in nonoccupationally exposed subjects. Thirty-one donors (16 male and 15 female, age range 5-74) provided serum and/or liver samples for analysis of PFOS and three other fluorochemicals: perfluorosulfonamide (PFOSA, C8F17SO2NH2), perfluorooctanoate (PFOA, C7F15CO2-), and perfluorohexanesulfonate (PFHxS, C6F13SO3-). Both sera and liver samples were extracted by ion-pair extraction and quantitatively assayed using high-performance liquid chromatography electrospray tandem mass spectrometry. Liver PFOS concentrations ranged from <4.5 ng/g (limit of quantitation, LOQ)to 57 ng/g. Serum PFOS concentrations ranged from <6.1 ng/mL (LOQ) to 58.3 ng/mL. Among the 23 paired samples, the mean liver to serum ratio was 1.3:1 (95% confidence interval 0.9:1-1.7:1). This liver to serum ratio is comparable to that reported in a toxicological study of cynomolgus monkeys, which had liver and serum concentrations 44595 orders of magnitude higher than observed in these human donors. This information may be useful in human risk characterization for PFOS. Liver to serum ratios were not estimated for PFOA, PFHxS, and PFOSA as 0.9 of the human donor liver samples were determined to be less than the LOQ.	●	●		●	●	●			●	-	1	A	A
189	ADME	Pan, Y.; Zhu, Y.; Zheng, T.; Cui, Q.; Buka, S. L.; Zhang, B.; Guo, Y.; Xia, W.; Yeung, L. W.; Li, Y.; Zhou, A.; Qiu, L.; Liu, H.; Jiang, M.; Wu, C.; Xu, S.; Dai, J.	Novel Chlorinated Polyfluorinated Ether Sulfonates and Legacy Per-/Polyfluoroalkyl Substances: Placental Transfer and Relationship with Serum Albumin and Glomerular Filtration Rate	2017	Environ Sci Technol. 2017 Jan 3;51(1):634-644. doi: 10.1021/acs.est.6b04590. Epub 2016 Dec 22.	Per- and polyfluoroalkyl substances (PFASs) may cross the placental barrier and lead to fetal exposure. However, little is known about the factors that influence maternal-fetal transfer of these chemicals. PFAS concentrations were analyzed in 100 paired samples of human maternal sera collected in each trimester and cord sera at delivery; these samples were collected in Wuhan, China, 2014 Linear regression was used to estimate associations of transfer efficiencies with factors. Chlorinated polyfluorinated ether sulfonates (Cl-PFAESs, 0.251388888888889 and 8:2) were frequently detected (>99%) in maternal and cord sera. A significant decline in PFAS levels during the three trimesters was observed. A U-shape trend for transfer efficiency with increasing chain length was observed for both carboxylates and sulfonates. Higher transfer efficiencies of PFASs were associated with advancing maternal age, higher education, and lower glomerular filtration rate (GFR). Cord serum albumin was a positive factors for higher transfer efficiency (increased 1.1-4.1% per 1g/L albumin), whereas maternal serum albumin tended to reduce transfer efficiency (decreased 2.4-4.3% per 1g/L albumin). Our results suggest that exposure to Cl-PFAESs may be widespread in China. The transfer efficiencies among different PFASs were structure-dependent. Physiological factors (e.g., GFR and serum albumin) were observed critical roles in PFAS placental transfer. for the first time to play	●	●								-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
190	ADME	Pennati, G.; Corno, C.; Costantino, M. L.; Bellotti, M.	Umbilical flow distribution to the liver and the ductus venosus in human fetuses during gestation: an anatomy-based mathematical modeling	2003	Med Eng Phys. 2003 Apr;25(3):229-38. doi: 10.1016/s1350-4533(02)00192-3.	The partitioning of umbilical vein blood flow between fetal liver and ductus venosus may be an indicator of the fetal well-being, because the goal of the ductus venosus is to supply oxygen and nutrients to heart and brain. Both distribution and blood flow rate of the umbilical vein are functions of the local vascular impedances that, in turn, depend on the anatomical features of the related vessels. In order to investigate the venous blood flows in human fetuses during a normal gestation, a simple lumped parameter mathematical model was developed on the basis of some information achievable by ultrasonographic techniques. Particularly, the diameter and length of umbilical vein and ductus venosus and the volume of the liver were used to derive the vascular impedances. Three different impedance models were adopted for the umbilical vein, the ductus venosus and the hepatic circulation. A linear model described viscous hydraulic dissipations through the umbilical vein, while a quadratic pressure-flow relationship was used for the ductus venosus due to the irregular local hemodynamics at its inlet. Finally, the equivalent impedance of the whole hepatic network was related to the hepatic volume assuming a tree-like, symmetric and self-similar fractal geometry. The hepatic vascular resistances predicted according to the fractal analysis were quite consistent with some experimental measurements in fetal lambs. In agreement with clinical observations, the model predicted blood flows through the ductus venosus and umbilical vein increasing (from about 25 to 75 ml/min and from about 45 to 370 ml/min, respectively) throughout the gestation (20-40 weeks), while the flow fraction shunted via the ductus venosus diminishes (from about 50 to 20%).	●	●								-		C	D
191	ADME	Pirali, Barbara; Negri, Sara; Chytiris, Spyridon; Perissi, Andrea; Villani, Laura; La Manna, Luigi; Cottica, Danilo; Ferrari, Massimo; Imbriani, Marcello; Rotondi, Mario; Chiovato, Luca	Perfluorooctane sulfonate and perfluorooctanoic acid in surgical thyroid specimens of patients with thyroid diseases	2009	Thyroid. 2009 Dec;19(12):1407-12. doi: 10.1089/thy.2009.0174.	BACKGROUND: Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) are ubiquitous compounds that may act as endocrine disruptors, neurotoxic agents, and fetal development perturbing substances and may also be carcinogenic, as recently demonstrated in experimental animal models. There is little information on the potential for these compounds to affect the thyroid. Therefore, this study was performed to measure the intrathyroidal levels of PFOA and PFOS in surgical specimens of thyroid glands and to determine if there was a relationship between the concentrations of these substances and the clinical, biochemical, and histologic phenotype of the patients from whom the thyroids were obtained. We also sought to determine if there was a relationship between tissue and serum levels of both PFOA and PFOS. METHODS: PFOA and PFOS were measured in 28 patients undergoing thyroid surgery for benign (15 multinodular goiters and 7 Graves' disease) and malignant (5 papillary and 1 follicular carcinoma) thyroid disorders. RESULTS: PFOA and PFOS were detectable in all surgical specimens of thyroid tissue. Their median concentrations were 2.0 ng/g (range = 0.4-4.6 ng/g) and 5.3 ng/g (range = 2.1-44.7), respectively. Intrathyroidal concentrations of PFOA and PFOS were similar in the thyroids of patients with thyroid diseases as in thyroid glands obtained at autopsy. There was no relationship between the intrathyroidal concentrations of either PFOA or PFOS and the underlying thyroid disease. A significant correlation between the serum and the tissue levels of PFOS was found in all patients. The serum concentrations of PFOA and PFOS were significantly higher than those in the correspondent surgical specimens. CONCLUSIONS: These observations do not support the view that PFOA and PFOS are actively concentrated in the thyroid. PFOA and PFOS, however, are both found in surgical and autopsy thyroid specimens. Therefore, further studies to determine if they have disrupting effects in thyroid cells or tissue, and studies to compare populations with and without these compounds in their thyroid glands, are important.	●	●			●	●				-		B	B
192	ADME	Pritchard, JA.	Changes in the blood volume during pregnancy and delivery [Review]	1965	Anesthesiology. 1965 Jul-Aug;26:393-9. doi: 10.1097/00000542-196507000-00004.	No abstract available	●	●								レビュー		D	D
193	ADME	Qin, Pengfei; Liu, Rutao; Pan, Xingren; Fang, Xiaoyan; Mou, Yue	Impact of carbon chain length on binding of perfluoroalkyl acids to bovine serum albumin determined by spectroscopic methods	2010	J Agric Food Chem. 2010 May 12;58(9):5561-7. doi: 10.1021/jf100412q.	Perfluoroalkyl acids (PFAAs), an emerging class of globally environmental contaminants, pose a great threat to humans with wide exposure from food and other potential sources. To evaluate the toxicity of PFAAs at the protein level, the effects of three PFAAs on bovine serum albumin (BSA) were characterized by fluorescence spectroscopy, synchronous fluorescence spectroscopy, and circular dichroism (CD). On the basis of the fluorescence spectra and CD data, we concluded that perfluoropentanoic acid (PFPA) had little effect on BSA. However, perfluorooctanoic acid (PFOA) and perfluorodecanoic acid (PFDA) exhibited remarkable fluorescence quenching, which was attributed to the formation of a moderately strong complex. The enthalpy change (DeltaH) and entropy change (DeltaS) indicated that van der Waals forces and hydrogen bonds were the dominant intermolecular forces in the binding of PFAAs to BSA. Furthermore, the BSA conformation was slightly altered in the presence of PFOA and PFDA, with a reduction of alpha helix. These results indicated that PFAAs indeed impact the conformation of BSA, and PFAAs with longer carbon chains were more toxic, especially at lower concentrations.	●	●								-		B	C
194	ADME	Reece, P.,.A.; Stafford, I.,.; Russell, J.,.; Gill, P.,.G.	Nonlinear renal clearance of ultrafilterable platinum in patients treated with cis-dichlorodiammineplatinum (II)	1985	Cancer Chemother Pharmacol. 1985;15(3):295-9. doi: 10.1007/BF00263904.	Nonlinear renal clearance of ultrafilterable platinum was observed in 5 of 7 patients given cis-dichlorodiammineplatinum (II) in doses of 50-140 mg/m2 by short-term infusion (2 h). Average renal clearance determined during and 24 h after infusion ranged from 100 to 543 ml/min and always exceeded creatinine clearance, suggesting that ultrafilterable platinum was renally secreted. Saturable tubular reabsorption was postulated on the basis that renal clearance was highest at peak plasma and urinary levels and fell as the levels declined. Although an overall relationship between dose and renal clearance was not apparent, one patient receiving the highest dose (140 mg/m2) had elevated average renal clearance (485 ml/min), probably associated with saturation of reabsorption, whereas a patient receiving 50 mg/m2 had the lowest average renal clearance (100 ml/min), indicating that either active secretion was lower, or tubular reabsorption was saturated. One patient also showed urine-flow-dependent changes in renal clearance. Four patients had transient rises in ultrafilterable platinum levels, which were attributed to changes in renal tubular reabsorption. The results suggest that renal clearance of ultrafilterable platinum is probably dependent on cis-DDP dose, urine flow rate, and individual variability in the extent of active secretion and tubular reabsorption. A sensitive HPLC method was applied and ultrafilterable platinum was detected in the plasma of all patients 24 h after infusion. Renal tubular reabsorption may result in prolonged plasma levels of ultrafilterable platinum, which could contribute to the drug's antitumour effect.	●	●								-		C	D
195	ADME	Rigden, Marc; Pelletier, Guillaume; Poon, Raymond; Zhu, Jiping; Auray-Blais, Christiane; Gagnon, René; Kubwabo, Cariton; Kosarac, Ivana; Lalonde, Kaela; Cakmak, Sabit; Xiao, Bin; Leingartner, Karen; Ku, Ka Lei; Bose, Ranjan; Jiao, Jianli	Assessment of urinary metabolite excretion after rat acute exposure to perfluorooctanoic acid and other peroxisomal proliferators	2015	Arch Environ Contam Toxicol. 2015 Jan;68(1):148-58. doi: 10.1007/s00244-014-0058-y.	Perfluorooctanoic acid (PFOA) is a persistent environmental contaminant. Activation of the peroxisome proliferator activated receptor alpha (PPARα) resulting from exposure to PFOA has been extensively studied in rodents. However, marked differences in response to peroxisome proliferators prevent extrapolation of rodent PPARα activation to human health risks and additional molecular mechanisms may also be involved in the biological response to PFOA exposure. To further explore the potential involvement of such additional pathways, the effects of PFOA exposure on urinary metabolites were directly compared with those of other well-known PPARα agonists. Male rats were administered PFOA (10, 33, or 100 mg/kg/d), fenofibrate (100 mg/kg/d), or di(2-ethylhexyl) phthalate (100 mg/kg/d) by gavage for 3 consecutive days and allowed to recover for 4 days, and overnight urine was collected. Greater urinary output was observed exclusively in PFOA-treated rats as the total fraction of PFOA excreted in urine increased with the dose administered. Assessment of urinary metabolites (ascorbic acid, quinolinic acid, 8-hydroxy-2'-deoxyguanosine, and malondialdehyde) provided additional information on PFOA's effects on hepatic glucuronic acid and tryptophan-nicotinamide adenine dinucleotide (NAD) pathways and on oxidative stress, whereas increased liver weight and palmitoyl-CoA oxidase activity indicative of PPARα activation and peroxisomal proliferation persisted up to day five after the last exposure.	●	●								-		-	B
196	ADME	Ruggiero, M. J.; Miller, H.; Idowu, J. Y.; Zitzow, J. D.; Chang, S. C.; Hagenbuch, B.	Perfluoroalkyl Carboxylic Acids Interact with the Human Bile Acid Transporter NTCP	2021	Livers. 2021 Dec;1(4):221-229. doi: 10.3390/livers1040017. Epub 2021 Oct 18.	Na+/taurocholate cotransporting polypeptide (NTCP) is important for the enterohepatic circulation of bile acids, which has been suggested to contribute to the long serum elimination half-lives of perfluoroalkyl substances in humans. We demonstrated that some perfluoroalkyl sulfonates are transported by NTCP; however, little was known about carboxylates. The purpose of this study was to determine if perfluoroalkyl carboxylates would interact with NTCP and potentially act as substrates. Sodium-dependent transport of [3H]-taurocholate was measured in human embryonic kidney cells (HEK293) stably expressing NTCP in the absence or presence of perfluoroalkyl carboxylates with varying chain lengths. PFCAs with 8 (PFOA), 9 (PFNA), and 10 (PFDA) carbons were the strongest inhibitors. Inhibition kinetics demonstrated competitive inhibition and indicated that PFNA was the strongest inhibitor followed by PFDA and PFOA. All three compounds are transported by NTCP, and kinetics experiments revealed that PFOA had the highest affinity for NTCP with a Km value of 1.8 ± 0.4 mM. The Km value PFNA was estimated to be 5.3 ± 3.5 mM and the value for PFDA could not be determined due to limited solubility. In conclusion, our results suggest that, in addition to sulfonates, perfluorinated carboxylates are substrates of NTCP and have the potential to interact with NTCP-mediated transport.	●	●								-		B	C
197	ADME	Russell, M. H.; Waterland, R. L.; Wong, F.	Calculation of chemical elimination half-life from blood with an ongoing exposure source: The example of perfluorooctanoic acid (PFOA)	2015	Chemosphere. 2015 Jun;129:210-6. doi: 10.1016/j.chemosphere.2014.07.061. Epub 2014 Aug 20.	Determination of the chemical clearance rate from human blood is a critical component of toxicokinetic exposure assessment. Analysis of temporal biomonitoring data without consideration of ongoing exposure results in calculation of apparent elimination half-life values that are longer than the intrinsic value. The intrinsic elimination half-life is solely a function of the rate of elimination while the apparent elimination half-life reflects the processes of both elimination and ongoing exposure. Confusion between intrinsic and apparent half-life values can lead to misinterpretation of biomonitoring data and can result in exaggerated predictions in subsequent modeling efforts. This work provides a review of the first-order equations that have been developed to calculate intrinsic and apparent half-life values and the potential bias that can result from confusing these two values. Published human biomonitoring data for perfluorooctanoic acid (PFOA) are analyzed using these equations to provide examples of low, medium and high bias in determination of the intrinsic elimination half-life from plasma or serum, the components of blood typically analyzed for PFOA. An approach is also provided to estimate the extent of exposure reduction that is indicated by declining longitudinal or cross-sectional biomonitoring data. Based on the evaluation methodology presented in this work, the intrinsic elimination half-life of PFOA in humans is 2.4years, representing the average of independent estimates of 2.5years (95% CI, 2.4-2.7) and 2.3years (95% CI, 2.1-2.4). The declining concentration of PFOA in blood of the general USA adult population represents an estimated exposure reduction of 20-30% over the period 1999-2008.	●	●								-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献①ラン	文献②ラン
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
198	ADME	Sakolish, C.; Chen, Z. W.; Dalaijamts, C.; Mitra, K.; Liu, Y. N.; Fulton, T.; Wade, T. L.; Kelly, E. J.; Rusyn, I.; Chiu, W. H. A.	Predicting tubular reabsorption with a human kidney proximal tubule tissue-on-a-chip and physiologically-based modeling	2020	Toxicol In Vitro. 2020 Mar;63:104752. doi: 10.1016/j.tiv.2019.104752. Epub 2019 Dec 17.	Kidney is a major route of xenobiotic excretion, but the accuracy of preclinical data for predicting in vivo clearance is limited by species differences and non-physiologic 2D culture conditions. Microphysiological systems can potentially increase predictive accuracy due to their more realistic 3D environment and incorporation of dynamic flow. We used a renal proximal tubule microphysiological device to predict renal reabsorption of five compounds: creatinine (negative control), perfluorooctanoic acid (positive control), cisplatin, gentamicin, and cadmium. We perfused compound-containing media to determine renal uptake/reabsorption, adjusted for non-specific binding. A physiologically-based parallel tube model was used to model reabsorption kinetics and make predictions of overall in vivo renal clearance. For all compounds tested, the kidney tubule chip combined with physiologically-based modeling reproduces qualitatively and quantitatively in vivo tubular reabsorption and clearance. However, because the in vitro device lacks filtration and tubular secretion components, additional information on protein binding and the importance of secretory transport is needed in order to make accurate predictions. These and other limitations, such as the presence of non-physiological compounds such as antibiotics and bovine serum albumin in media and the need to better characterize degree of expression of important transporters, highlight some of the challenges with using microphysiological devices to predict in vivo pharmacokinetics.	●	●							-		B	C
199	ADME	Sanchez Garcia, D.; Sjödin, M.; Hellstrandh, M.; Norinder, U.; Nikiforova, V.; Lindberg, J.; Wincent, E.; Bergman, Å.; Cotgreave, I.; Munic Kos, V.	Cellular accumulation and lipid binding of perfluorinated alkylated substances (PFASs) - A comparison with lysosomotropic drugs	2018	Chem Biol Interact . 2018 Feb 1;281:1-10. doi: 10.1016/j.cbi.2017.12.021. Epub 2017 Dec 14.	Many chemicals accumulate in organisms through a variety of different mechanisms. Cationic amphiphilic drugs (CADs) accumulate in lysosomes and bind to membranes causing phospholipidosis, whereas many lipophilic chemicals target adipose tissue. Perfluoroalkyl substances (PFASs) are widely used as surfactants, but many of them are highly bioaccumulating and persistent in the environment, making them notorious environmental toxicants. Understanding the mechanisms of their bioaccumulation is, therefore, important for their regulation and substitution with new, less harmful chemicals. We compared the highly bioaccumulative perfluorooctanesulfonic acid PFOS to its three less bioaccumulative alternatives perfluorooctanoic acid (PFOA), perfluorohexanoic acid (PFHxA) and perfluorobutane sulfonic acid (PFBS), in their ability to accumulate and remain in lung epithelial cells (NCI-H292) and adipocytes (3T3-L1K) in vitro. As a reference point we tested a set of cationic amphiphilic drugs (CADs), known to highly accumulate in cells and strongly bind to phospholipids, together with their respective non-CAD controls. Finally, all compounds were examined for their ability to bind to neutral lipids and phospholipids in cell-free systems. Cellular accumulation and retention of the test compounds were highly correlated between the lung epithelial cells and adipocytes. Interestingly, although an anion itself, intensities of PFOS accumulation and retention in cells were comparable to those of CAD compounds, but PFOS failed to induce phospholipidosis or alter lysosomal volume. Compared to other lipophilicity measures, phospholipophilicity shows the highest correlation ($R^2 = 0.75$) to cellular accumulation data in both cell types and best distinguishes between high and low accumulating compounds. This indicates that binding to phospholipids may be the most important component in driving high cellular accumulation in lung epithelial cells, as well as in adipocytes, and for both CADs and bioaccumulating PFASs. Obtained continuous PLS models based on compound's affinity for phospholipids and neutral lipids can be used as good prediction models of cellular accumulation and retention of PFASs and CADs.	●	●							-		B	C
200	ADME	Schulz, Katarina; Silva, Marcia R; Klaper, Rebecca	Distribution and effects of branched versus linear isomers of PFOA, PFOS, and PFHxS: A review of recent literature [Review]	2020	Sci Total Environ. 2020 Sep 1;733:139186. doi: 10.1016/j.scitotenv.2020.139186. Epub 2020 May 4.	Perfluorinated alkyl substances (PFAS) have come to attention recently due to their widespread presence in the environment, recalcitrance, and potential negative health associations. Because of the long-term production of PFAS using ECF, which created branched isomers as byproducts in addition to the intended linear product, branched isomers of PFAS account for a significant portion of PFAS load in the environment. The distribution of isomers is not consistent in the environment, however. Geographic location appears to be a major factor in determining the isomer makeup of PFAS in surface and groundwater as well as in humans and animals. This is largely to differences in production methods; a region that produced PFAS via ECF for many years would have a higher ratio of branched isomers than one that produces PFAS using telomerization. In addition, the different structures of branched PFAS isomers as compared to linear PFAS appear to affect transport in the environment. Research suggests that linear PFAS sorb preferentially to soil and sediments, whereas branched isomers are more likely to remain in water. The higher polarity of the branched structure explains this difference. Studies in humans and animals show that most animals preferentially accumulate the linear PFOS isomer, but humans appear to preferentially accumulate the branched isomers as they are often found in human serum at percentages higher than that of ECF product. In addition, some studies have indicated that linear and branched PFAS isomers have some unique negative health associations. Very few studies, however, account for linear and branched PFAS separately.	●	●							-		B	B
201	ADME	Sheng, N.; Cui, R.; Wang, J.; Guo, Y.; Wang, J.; Dai, J.	Cytotoxicity of novel fluorinated alternatives to long-chain perfluoroalkyl substances to human liver cell line and their binding capacity to human liver fatty acid binding protein	2018	Arch Toxicol. 2018 Jan;92(1):359-369. doi: 10.1007/s00204-017-2055-1. Epub 2017 Sep 1.	Although shorter chain homologues and other types of fluorinated chemicals are currently used as alternatives to long-chain perfluoroalkyl substances (PFASs), their safety information remains unclear and urgently needed. Here, the cytotoxicity of several fluorinated alternatives (i.e., 6:2 fluorotelomer carboxylic acid (6:2 FTCA), 6:2 fluorotelomer sulfonic acid (6:2 FTSA), 6:2 chlorinated polyfluorinated ether sulfonate (6:2 Cl-PFESA), and hexafluoropropylene oxide (HFPO) homologues) to human liver HL-7702 cell line were measured and compared with perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS). Their binding mode and affinity to human liver fatty acid binding protein (hL-FABP) were also determined. Compared with PFOA and PFOS, 6:2 Cl-PFESA, HFPO trimer acid (HFPO-TA), HFPO tetramer acid (HFPO-TeA), and 6:2 FTSA showed greater toxic effects on cell viabilities. At low exposure doses, these alternatives induced cell proliferation with similar mechanism which was different from that of PFOA and PFOS. Furthermore, binding affinity to hL-FABP decreased in the order of 6:2 FTCA < 6:2 FTSA < HFPO dimer acid (HFPO-DA) < PFOA < PFOS/6:2 Cl-PFESA/HFPO-TA. Due to their distinctive structure, 6:2 Cl-PFESA and HFPO homologues were bound to the hL-FABP inner pocket with unique binding modes and higher binding energy compared with PFOA and PFOS. This research enhances our understanding of the toxicity of PFAS alternatives during usage and provides useful evidence for the development of new alternatives.	●	●							-		C	B
202	ADME	Sheng, N.; Wang, J.; Guo, Y.; Wang, J.; Dai, J.	Interactions of perfluorooctanesulfonate and 6:2 chlorinated polyfluorinated ether sulfonate with human serum albumin: A comparative study	2020	Chem Res Toxicol. 2020 Jun 15;33(6):1478-1486. doi: 10.1021/acs.chemrestox.0c00075. Epub 2020 May 22.	6:2 Chlorinated polyfluorinated ether sulfonate (6:2 Cl-PFESA) possesses a similar structure to perfluorooctanesulfonate (PFOS) and is the third most important polyfluoroalkyl/perfluoroalkyl substance (PFAS) found in the general population of China. Studies have indicated that 6:2 Cl-PFESA exhibits a stronger bioaccumulative and toxicological potential than PFOS and is thus of considerable environmental concern. Here, the binding characteristics of PFOS and 6:2 Cl-PFESA to human serum albumin (HSA) were explored based on in vitro and in silico methods. In the cell uptake assays, supplementation of HSA in the culture medium hindered diffusion of PFOS and 6:2 Cl-PFESA from the medium into cells. With the addition of 0.5, 10, and 200 μM HSA in the culture medium, the PFOS concentration in cells decreased by 21.4%, 78.1%, and 92.8%, whereas the 6:2 Cl-PFESA concentration in cells decreased by 28.4%, 84.4%, and 93.9%, respectively. Although no statistically significant difference between the reduction of PFOS and 6:2 Cl-PFESA was observed with 200 μM HSA in medium, the significant decrease in cellular 6:2 Cl-PFESA than PFOS after addition of 0.5 and 10 μM HSA implied that 6:2 Cl-PFESA had a stronger binding affinity than PFOS to HSA. Ultrafiltration centrifugation also suggested that 6:2 Cl-PFESA (Kd = 16.7 μM) had a higher affinity than PFOS (Kd = 30.7 μM) to HSA, though the binding molar ratios were similar, with 1 M HSA binding to 3-4 M PFOS/6:2 Cl-PFESA. Limited proteolysis further identified the core HSA peptides that bind to PFOS (peptide II, aa 189-457) and 6:2 Cl-PFESA (peptide I, aa 39-310). Using purified core peptides, 6:2 Cl-PFESA showed a stronger binding affinity than PFOS to both peptides I and II. The binding modes indicated that the chlorine and oxygen atoms in 6:2 Cl-PFESA were likely responsible for its preferential binding to Sudlow site I than to Trp214 or Sudlow site II, with the latter being the optimal binding site for PFOS. Overall, the stronger binding affinity of 6:2 Cl-PFESA to HSA may contribute to its higher bioaccumulation potential than PFOS.	●	●							-		B	B
203	ADME	Smith, E.; Weber, J.; Rofe, A.; Gancarz, D.; Naidu, R.; Juhasz, A. L.	Assessment of DDT Relative Bioavailability and Bioaccessibility in Historically Contaminated Soils Using an in Vivo Mouse Model and Fed and Unfed Batch in Vitro Assays	2012	Environ Sci Technol. 2012 Mar 6;46(5):2928-34. doi: 10.1021/es203030q. Epub 2012 Feb 22.	In this study, DDTr (DDTr = DDT + DDD + DDE) relative bioavailability in historically contaminated soils (n = 7) was assessed using an in vivo mouse model. Soils or reference materials were administered to mice daily over a 7 day exposure period with bioavailability determined using DDTr accumulation in adipose, kidney, or liver tissues. Depending on the target tissue used for its calculation, some variability in DDTr relative bioavailability was observed; however, it did not exceed 0.25 (range 2-25%). When DDTr bioaccessibility was determined using organic physiologically based extraction test (Org-PBET), unified BARGE method (UBM), and fed organic estimation human simulation test (FOREhST) in vitro assays, bioaccessibility was less than 0.04 irrespective of the assay utilized and the concentration of DDTr in the contaminated soil. Pearson correlations demonstrate a poor relationship between DDTr relative bioavailability and DDTr bioaccessibility (0.47, 0.38, and 0.28, respectively), illustrating the limitations of the static in vitro methods for predicting the dynamic processes of the mammalian digestive system for this hydrophobic organic contaminant.	●	●							-		C	D
204	ADME	Tan, Y. M.; Clewell, H. J.; Andersen, M. E.	Time dependencies in perfluorooctylacids disposition in rat and monkeys: a kinetic analysis	2008	Toxicol Lett. 2008 Feb 28;177(1):38-47. doi: 10.1016/j.toxlet.2007.12.007. Epub 2007 Dec 27.	Perfluorooctanoate (PFOA) and perfluorooctanesulfonate (PFOS) are surfactants that have been used for various industrial and consumer applications. The widespread exposure and persistence of PFOA and PFOS in humans have caused these chemicals to be the subject of intense kinetic and toxicity studies. To identify the biological determinants of the species different in elimination observed in kinetic studies, we incorporated time-dependent descriptions for free fraction in plasma and for volume of distribution into an earlier pharmacokinetic model to simulate the time course behaviors of PFOA and PFOS in monkeys and rats. The structurally similar model for monkeys and rats also allows for examination of the complex kinetics observed in animal studies. A higher estimated liver:blood partition coefficient in the rat and additional binding in rat liver suggest that PFOS retention in liver occurs in rats but not in monkeys. Higher liver:blood partition coefficient and renal filtration suggest that PFOS is retained longer in tissues compared to PFOA. A much lower renal resorption may explain the fast elimination of PFOA from plasma observed in female compared to male rats. Understanding these cross-species, cross-compound, and cross-gender difference is an important step in the future development of a human model for these compounds.	●	●		●	●	●			-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献ランク①	文献ランク②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
205	ADME	Tao, L.; Kannan, K.; Wong, C. M.; Arcaro, K. F.; Butenhoff, J. L.	Perfluorinated compounds in human milk from Massachusetts, USA	2008	Environ Sci Technol. 2008 Apr 15;42(8):3096-101. doi: 10.1021/es702789k.	Perfluorinated compounds (PFCs), notably perfluorooctanesulfonate (PFOS) and perfluorooctanoic acid (PFOA), have been reported in human blood. Furthermore, the occurrence of PFCs in the blood of newborn babies, coupled with the need to study the potential association of PFC exposure with birth outcomes in neonates, suggests the need for determining the sources and magnitude of exposure in infants. In this study, nine PFCs were measured in 45 human breast milk samples collected in 2004 from Massachusetts, U.S.A. PFOS and PFOA were the predominant PFCs found at mean concentrations of 131 and 43.8 pg/mL, respectively. Comparison of the ratio of PFOS to PFOA in human milk with the ratios published for human serum from the U.S. female population suggested preferential partitioning of PFOA to milk. Concentrations of PFOA were significantly higher in the milk of mothers nursing for the first time (n = 34) than in the milk of mothers who have previously nursed (n = 8). Based on the estimated body weight and milk intake, the average and highest daily intakes of total PFCs by infants were 23.5 and 87.1 ng/kg bw, respectively. We found that the daily ingestion rates of PFOS and PFOA did not exceed the tolerable daily intake recommended by the U.K. Food Standards Agency. This is the first study to measure the occurrence of PFCs in human milk from the U.S.A.	●	●		●	●	●				-		B	A
206	ADME	Tilston, E. L.; Gibson, G. R.; Collins, C. D.	Colon extended physiologically based extraction test (CE-PBET) increases bioaccessibility of soil-bound PAH	2011	Environ Sci Technol. 2011 Jun 15;45(12):5301-8. doi: 10.1021/es2004705. Epub 2011 May 13.	Assessment of the risk to human health posed by contaminated land may be seriously overestimated if reliant on total pollutant concentration. In vitro extraction tests, such as the physiologically based extraction test (PBET), imitate the physicochemical conditions of the human gastro-intestinal tract and offer a more practicable alternative for routine testing purposes. However, even though passage through the colon accounts for approximately 0.8 of the transit time through the human digestive tract and the typical contents of the colon in vivo are a carbohydrate-rich aqueous medium with the potential to promote desorption of organic pollutants, PBET comprises stomach and small intestine compartments only. Through addition of an eight-hour colon compartment to PBET and use of a carbohydrate-rich fed-state medium we demonstrated that colon-extended PBET (CE-PBET) increased assessments of soil-bound PAH bioaccessibility by up to 0.5 in laboratory soils and a factor of 4 in field soils. We attribute this increased bioaccessibility to a combination of the additional extraction time and the presence of carbohydrates in the colon compartment, both of which favor PAH desorption from soil. We propose that future assessments of the bioaccessibility of organic pollutants in soils using physiologically based extraction tests should have a colon compartment as in CE-PBET.	●	●								-		C	D
207	ADME	Wan, Hin Ting; Wong, Aman Yi-Man; Feng, Shi; Wong, Chris Kong-Chu	Effects of In Utero Exposure to Perfluorooctane Sulfonate on Placental Functions	2020	Environ Sci Technol. 2020 Dec 15;54(24):16050-16061. doi: 10.1021/acs.est.0c06569. Epub 2020 Dec 1.	Perfluorooctane sulfonate (PFOS) is a metabolic-disrupting chemical. There is a strong association between maternal and cord blood PFOS concentrations, affecting metabolism in early life. However, the underlying effects have not been fully elucidated. In this study, using the maternal-fetal model, we investigated the impact of gestational PFOS exposure on the placental structure and nutrient transport. Pregnant mice were oral gavaged with PFOS (1 or 3 μg PFOS/g body weight) from gestational day (GD) 4.5 until GD 17.5. Our data showed a significant reduction in fetal body weight at high dose exposure. There were no noticeable changes in placental weights and the relative areas of junctional and labyrinth zones among the control and exposed groups. However, a placental nutrient transport assay showed a significant reduction in maternal-fetal transport of the glucose and amino acid analogues. Western blot analysis showed a significant decrease in the expression levels of placental SNAT4 upon PFOS exposure. Moreover, in the high-dose exposed group, placenta and fetal livers were found to have significantly higher corticosterone levels, a negative regulator of fetal growth. The perturbation in the placental transport function and corticosterone levels accounted for the PFOS-induced reduction of fetal body weights.	●	●								-		-	B
208	ADME	Wang, J.; Pan, Y.; Cui, Q.; Yao, B.; Wang, J.; Dai, J.	Penetration of PFASs across the blood cerebrospinal fluid barrier and its determinants in humans	2018	Environ Sci Technol. 2018 Nov 20;52(22):13553-13561. doi: 10.1021/acs.est.8b04550. Epub 2018 Nov 7.	Laboratory studies indicate that exposure to perfluoroalkyl and polyfluoroalkyl substances (PFASs) can induce neurobehavioral effects in animals. However, the penetration of PFASs across the brain barrier and its determining factors are yet to be clarified in humans. We studied PFAS levels in 223 matched-pair serum and cerebrospinal fluid (CSF) samples from hospital in-patients using UPLC/MS/MS. Among the 21 target analytes, PFOA, PFOS, and 0.251388888888889 Cl-PFESA were dominant in serum, with mean concentrations of 7.4, 6.8, and 6.2 ng/mL, respectively, contributing 0.79 to the total PFAS burden in serum. In CSF, PFOA, PFOS, and 0.251388888888889 Cl-PFESA were again the dominant PFASs, with mean concentrations of 0.078, 0.028, and 0.051 ng/mL contributing 36%, 13%, and 24%, respectively, to the total PFAS burden in CSF. Furthermore, PFAS penetration (RPFAS, PFASCSF/PFASserum) was positively correlated with the barrier permeability index RAlb (AlbuminCSF/Albuminserum), indicating that barrier integrity was the main determinant of PFAS penetration across the blood-CSF barrier. Positive associations between the RPFAS values of the main PFASs and serum C-reactive protein were observed, implying that inflammation facilitates the penetration of PFASs across the brain barrier.	●	●								-		B	B
209	ADME	Wang, Yiwen; Han, Wenchao; Wang, Caifeng; Zhou, Yijun; Shi, Rong; Bonefeld-Jørgensen, Eva Cecilie; Yao, Qian; Yuan, Tao; Gao, Yu; Zhang, Jun; Tian, Ying	Efficiency of maternal-fetal transfer of perfluoroalkyl and polyfluoroalkyl substances	2019	Environ Sci Pollut Res Int. 2019 Jan;26(3):2691-2698. doi: 10.1007/s11356-018-3686-3. Epub 2018 Nov 27.	Perfluoroalkyl and polyfluoroalkyl substances (PFASs) can be transferred from a mother to her fetus during pregnancy and adversely affect fetal development. However, the efficiency and influencing factors of PFASs maternal-fetal transfer remain unclear. We measured the levels of six perfluoroalkylcarboxylates, three perfluoroalkylsulfonates, and one sulfonamide in 369 pairs of maternal and umbilical cord serum and examined the transplacental transfer efficiency (TTE) of PFASs by the functional group and carbon chain length in a prospective birth cohort in Shandong, China. All ten PFASs were detected in both maternal and umbilical cord serum in nearly all samples. Maternal and cord levels were closely correlated (the correlation coefficient [r] ranging from 0.485 to 0.908) in most PFASs except perfluorobutane sulfonic acid (PFBS) (r ＝ 0.159). TTE was significantly affected by the functional group and carbon chain length. Compared to perfluoroalkylcarboxylates, perfluoroalkylsulfonates had a lower ratio of maternal to fetal transfer. A U-shaped relationship between carbon chain length and TTE was observed for perfluoroalkylcarboxylates while a monotonic descending trend was identified between TTE and the increasing carbon chain length for perfluoroalkylsulfonates. PFASs can readily pass through the placenta. The functional group and carbon chain length are important determinants for the TTE of PFASs.	●	●								-		B	B
210	ADME	Wimsatt, J.; Villers, M.; Thomas, L.; Kamarec, S.; Montgomery, C.; Yeung, L. W.; Hu, Y.; Innes, K.	Oral perfluorooctane sulfonate (PFOS) lessens tumor development in the APC(min) mouse model of spontaneous familial adenomatous polyposis	2016	BMC Cancer. 2016 Dec 8;16(1):942. doi: 10.1186/s12885-016-2861-5.	BACKGROUND: Colorectal cancer is the second most common cause of cancer deaths for both men and women, and the third most common cause of cancer in the U.S. Toxicity of current chemotherapeutic agents for colorectal cancer, and emergence of drug resistance underscore the need to develop new, potentially less toxic alternatives. Our recent cross-sectional study in a large Appalachian population, showed a strong, inverse, dose-response association of serum perfluorooctane sulfonate (PFOS) levels to prevalent colorectal cancer, suggesting PFOS may have therapeutic potential in the prevention and/or treatment of colorectal cancer. In these preliminary studies using a mouse model of familial colorectal cancer, the APC(min) mouse, and exposures comparable to those reported in human populations, we assess the efficacy of PFOS for reducing tumor burden, and evaluate potential dose-response effects.METHODS: At 44687 weeks of age, APC(min) mice were randomized to receive 0, 20, 250 mg PFOS/kg (females) or 0, 10, 50 and 200 mg PFOS/kg (males) via their drinking water. At 15 weeks of age, gastrointestinal tumors were counted and scored and blood PFOS levels measured.RESULTS: PFOS exposure was associated with a significant, dose-response reduction in total tumor number in both male and female mice. This inverse dose-response effect of PFOS exposure was particularly pronounced for larger tumors (r(2) for linear trend ＝ 0.44 for males, p's <0.001).CONCLUSIONS: The current study in a mouse model of familial adenomatous polyposis offers the first experimental evidence that chronic exposure to PFOS in drinking water can reduce formation of gastrointestinal tumors, and that these reductions are both significant and dose-dependent. If confirmed in further studies, these promising findings could lead to new therapeutic strategies for familial colorectal cancer, and suggest that PFOS testing in both preventive and therapeutic models for human colorectal cancer is warranted.	●	●								-		-	C
211	ADME	Xu, Y.; Fletcher, T.; Pineda, D.; Lindh, C. H.; Nilsson, C.; Glynn, A.; Vogs, C.; Norström, K.; Lilja, K.; Jakobsson, K.; Li, Y.	Serum Half-Lives for Short- and Long-Chain Perfluoroalkyl Acids after Ceasing Exposure from Drinking Water Contaminated by Firefighting Foam	2020	Environ Health Perspect. 2020 Jul;128(7):77004. doi: 10.1289/EHP6785. Epub 2020 Jul 10.	BACKGROUND: Firefighting foam-contaminated ground water, which contains high levels of perfluoroalkyl substances (PFAS), is frequently found around airports. In 2018 it was detected that employees at a municipal airport in northern Sweden had been exposed to high levels of short-chain PFAS along with legacy PFAS (i.e., PFOA, PFHxS, and PFOS) through drinking water.OBJECTIVES: In this study, we aimed to describe the PFAS profile in drinking water and biological samples (paired serum and urine) and to estimate serum half-lives of the short-chain PFAS together with legacy PFAS.METHODS: Within 2 weeks after provision of clean water, blood sampling was performed in all 26 airport employees. Seventeen of them were then followed up monthly for 5 months. PFHxA, PFHpA, PFBS, PFPeS, and PFHpS together with legacy PFAS in water and biological samples were quantified using LC/MS/MS. Half-lives were estimated by assuming one compartment, first-order elimination kinetics.RESULTS: The proportions of PFHxA, PFHpA, and PFBS were higher in drinking water than in serum. The opposite was found for PFHxS and PFOS. The legacy PFAS accounted for about 0.5 of total PFAS in drinking water and 0.9 in serum. Urinary PFAS levels were very low compared with serum. PFBS showed the shortest half-life {average 44 d [95% confidence interval (CI): 37, 55 d]}, followed by PFHpA [62 d (95% CI: 51, 80 d)]. PFPeS and PFHpS showed average half-lives as 0.63 and 1.46 y, respectively. Branched PFOS isomers had average half-lives ranging from 1.05 to 1.26 y for different isomers. PFOA, PFHxS, and linear PFOS isomers showed average half-lives of 1.77, 2.87, and 2.93 y, respectively.DISCUSSION: A general pattern of increasing half-lives with increasing chain length was observed. Branched PFOS isomers had shorter half-lives than linear PFOS isomers.	●	●							●	-		A	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報抽出対象	文献ランク①	文献ランク②
212	ADME	Yang, C.; Lee, H. K.; Zhang, Y.; Jiang, L. L.; Chen, Z. F.; Chung, A. C. K.; Cai, Z.	In Situ Detection and Imaging of PFOS in Mouse Kidney by Matrix-Assisted Laser Desorption/Ionization Imaging Mass Spectrometry	2019	Anal Chem. 2019 Jul 16;91(14):8783-8788. doi: 10.1021/acs.analchem.9b00711. Epub 2019 Jun 28.	Perfluorooctanesulfonic acid (PFOS) is an emerging environmental organic pollutant that has been widely used in daily life products in the last century. Numerous studies showed that the accumulation of PFOS in human through food chain would lead to various disease. However, there is currently no report about its in situ localization in the tissue. In present study, we aimed to develop a reproductive and less-cost method to quantitatively detect and determine the spatial distribution of PFOS in mouse kidney by matrix-assisted laser desorption/ionization imaging mass spectrometry (MALDI-IMS) with a commercially available matrix. α-Cyano-4-hydroxycinnamic acid (CHCA) matrix was optimized for PFOS detection in MALDI-IMS analysis. Compared to other organic matrices, CHCA used in negative ion mode showed less background interference and enhanced MS signal intensity and high spatial resolution (80 μm) for PFOS analysis. The use of a CHCA matrix with an autospray system led to successful identification of the PFOS ion signals on the perfusion kidney tissue. The detection limit was at the μg/mL level, with direct visualization from a MS image. The developed method with the optimized parameters was successfully employed to obtain the PFOS spatial distribution in the kidney collected from mice after the PFOS exposure for 14 days. PFOS was mainly distributed in the kidney cortex region, which was consistent with the histological analysis results. Taken together, a rapid, economic, and efficient method was developed for PFOS detection by MALDI-IMS using a CHCA matrix. Mapping the distribution of PFOS by MALDI-IMS with a CHCA matrix provides an innovative approach for the analysis of environmental pollutants in animal or human tissues.	●	●								-		B	B
213	ADME	Yang, C. H.; Glover, K. P.; Han, X.	Organic anion transporting polypeptide (Oatp) 1a1-mediated perfluorooctanoate transport and evidence for a renal reabsorption mechanism of Oatp1a1 in renal elimination of perfluorocarboxylates in rats	2009	Toxicol Lett. 2009 Oct 28;190(2):163-71. doi: 10.1016/j.toxlet.2009.07.011. Epub 2009 Jul 16.	Organic anion transporting polypeptide (Oatp) 1a1 has been hypothesized to play a key role in rat renal reabsorption of perfluorooctanoate (PFO). We have investigated PFO uptake kinetics in Chinese Hamster Ovary (CHO) cells that have been stably transfected with the cDNA encoding Oatp1a1. The Oatp1a1-expressing CHO cells have been validated by their Oatp1a1 gene expression, estrone-3-sulfate (E3S) uptake kinetics, and the correlation between Oatp1a1 gene expression and E3S uptake activity that were both induced by the treatment of sodium butyrate. Oatp1a1-mediated PFO uptake underwent a saturable process with a K(m) value of 162.2+/-20.2microM, which was effectively inhibited by known Oatp1a1 substrates sulfobromophthalein and taurocholate, and a major flavonoid in grapefruit juice, naringin. The inhibition of Oatp1a1-mediated E3S uptake has been compared for linear perfluorocarboxylates with carbon chain lengths ranged from 4 to 12 There was no apparent inhibition by perfluorobutanoate and perfluoropentanoate at 1mM. Inhibition was observed for perfluorohexanoate at 1mM and the level of inhibition increased as the increase of the chain length up to perfluorodecanoate. The values of apparent inhibition constant (K(i,app)) were determined for perfluorocarboxylates with chain lengths between 6 and 10 The log values of K(i,app) exhibited a negative linear relationship to the chain lengths and a positive linear relationship to the log values of the total clearance of perfluorocarboxylates in male rats. This in vitro-to-in vivo correlation strongly supports a tubular reabsorptive role of Oatp1a1 in rat renal elimination of perfluorocarboxylates. Due to the sex-dependent expression of Oatp1a1 in rat kidney, Oatp1a1-mediated tubular reabsorption is suggested to be the mechanism for the sex-dependent renal elimination of PFO in rats.	●	●				●				-		B	B
214	ADME	Yang, D.; Han, J.; Hall, D. R.; Sun, J.; Fu, J.; Kutarna, S.; Houck, K. A.; Lalone, C. A.; Doering, J. A.; Ng, C. A.; Peng, H.	Nontarget Screening of Per- and Polyfluoroalkyl Substances Binding to Human Liver Fatty Acid Binding Protein	2020	Environ Sci Technol. 2020 May 5;54(9):5676-5686. doi: 10.1021/acs.est.0c00049. Epub 2020 Apr 16.	More than one thousand per- and polyfluoroalkyl substances (PFASs) have been discovered by nontarget analysis (NTA), but their prioritization for health concerns is challenging. We developed a method by incorporating size exclusion column co-elution (SECC) and NTA, to screen PFASs binding to human liver fatty acid binding protein (hL-FABP). Of 74 PFASs assessed, 20 were identified as hL-FABP ligands in which 8 of them have high binding affinities. Increased PFASs binding affinities correlate with stronger responses in electrospray ionization (ESI-) and longer retention times on C18 column. This is well explained by a mechanistic model which revealed that both polar and hydrophobic interactions are crucial for binding affinities. Encouraged by this, we then developed a SECC method to identify hL-FABP ligands, and all 8 high-affinity ligands were selectively captured from 74 PFASs. The method was further applied to an aqueous film-forming foam (AFFF) product in which 31 new hL-FABP ligands were identified. Suspect and nontargeted screening revealed these ligands as analogues of perfluorosulfonic acids, and homologues of alkyl ether sulfates (C8- and C10/EOn, C8H17(C2H4O)nSO4- and C10H21(C2H4O)nSO4-). The SECC method was then applied to AFFF-contaminated surface waters. In addition to perfluorooctanesulfonic acid (PFOS) and perfluorohexanesulphonic acid (PFHxS), 8 other AFFF chemicals were discovered as novel ligands, including four C14- and C15/EOn. This study implemented a high-throughput method to prioritize PFASs and revealed the existence of many previously unknown hL-FABP ligands.	●	●								-		B	B
215	ADME	Ylinen, M.; Kojo, A.; Hanhijärvi, H.; Peura, P.	Disposition of perfluorooctanoic acid in the rat after single and subchronic administration	1990	Bull Environ Contam Toxicol. 1990 Jan;44(1):46-53. doi: 10.1007/BF01702360.	No abstract available	●	●		●		●				-		B	D
216	ADME	Yu, W. G.; Liu, W.; Liu, L.; Jin, Y. H.	Perfluorooctane sulfonate increased hepatic expression of OAPT2 and MRP2 in rats	2011	Arch Toxicol. 2011 Jun;85(6):613-21. doi: 10.1007/s00204-010-0613-x. Epub 2010 Nov 3.	The toxicity of perfluorooctane sulfonate (PFOS), a persistent organic compound, is of great concern. Several studies have reported that PFOS decreases circulating thyroid hormone (TH) concentrations. However, the mechanisms involved remain to be determined. Female rats were exposed to -1 vehicle; -2 PFOS (0.2, 1.0, and 3 mg/kg); -3 propylthiouracil (PTU, 10 mg/kg); or -4 PTU (10 mg/kg) + PFOS (3.0 mg/kg) by gavage once a day for 5 consecutive days. Parameters including contents of total T4 (TT4) and total T3 (TT3) in both serum and bile, serum concentrations of transthyretin and thyroglobulin, as well as transcripts of transporters involved in hepatic uptake and efflux of T4 were determined in control and PFOS-exposed groups. TT4 and TT3 were also analyzed in PTU and PTU + PFOS groups in order to reflect the different hormone effects between PFOS, PTU, and PFOS + PTU. Results showed that serum TT4 and TT3 decreased, while bile TT4 and TT3 remained stable following PFOS exposure. Exposure to 3 mg/kg of PFOS significantly enhanced hepatic organic anion transporter OATP2 mRNA expression (1.43 times of control). Treatment with PFOS increased hepatic expression of multidrug resistance--associated protein MRP2, approximately 1.8 and 1.69 times of control in 1 and 3 mg/kg groups, respectively. Spearman's correlation coefficients revealed that MRP2 mRNA expression correlated well with serum TT4 level (r = -0.528, P = 0.012). Serum thyroglobulin and transthyretin levels remained stable. Serum TT3, bile TT4, and bile TT3 were significantly different between PFOS and PTU groups. No significant differences of TT4 and TT3 in both serum and bile were observed between PTU and PTU + PFOS (P > 0.05). In conclusion, PFOS increased hepatic expression of OAPT2, which could possibly enhance hepatic uptake and metabolism of T4 in rats. PFOS-induced TT4 deficiency is mainly due to the extrathyroidal metabolism of T4, which is probably different from the classic goitrogen, PTU.	●	●								-		A	C
217	ADME	Zaïr, Z. M.; Eloranta, J. J.; Stieger, B.; Kullak-Ublick, G. A.	Pharmacogenetics of OATP (SLC21/SLCO), OAT and OCT (SLC22) and PEPT (SLC15) transporters in the intestine, liver and kidney	2008	Pharmacogenomics. 2008 May;9(5):597-624. doi: 10.2217/14622416.9.5.597.	The role of carrier-mediated transport in determining the pharmacokinetics of drugs has become increasingly evident with the discovery of genetic variants that affect expression and/or function of a given drug transporter. Drug transporters are expressed at numerous epithelial barriers, such as intestinal epithelial cells, hepatocytes, renal tubular cells and at the blood-brain barrier. Several recent studies have associated alterations in substrate uptake with the presence of SNPs. Here, we summarize the current knowledge on the functional and phenotypic consequences of genetic variation in intestinally, hepatically and renally expressed members of the organic anion-transporting polypeptide family (OATPs; SLC21/SLCO family), the organic anion and organic cation transporters (OATs/OCTs; SLC22 family) and the peptide transporter-1 (PEPT1; SLC15 family).	●	●								-		C	C
218	ADME	Zhang, R.; Zhang, H.; Chen, B.; Luan, T.	Fetal bovine serum attenuating perfluorooctanoic acid-inducing toxicity to multiple human cell lines via albumin binding	2020	J Hazard Mater. 2020 May 5;389:122109. doi: 10.1016/j.jhazmat.2020.122109. Epub 2020 Jan 21.	Perfluorooctanoic acid (PFOA), as a typical emerging organic pollutant, can interact with serum albumin. However, it remains to characterize the binding of PFOA with serum albumin and to address the role of this interaction in related toxic effects. We aimed to characterize the interaction between PFOA and albumin for understanding the effects of this interaction on the uptake, distribution, and toxicity of PFOA in human cells. The results showed that viable cell count was significantly enhanced by addition of fetabl bovine serum (FBS) into cell culture medium with 300 μM PFOA treatment. PFOA mainly existed as complexed with FBS, at FBS concentration > 10%, which substantially reduced the absorption efficiency of all cell lines to PFOA. The majority of PFOA was accumulated in the cytosolic fraction, followed by nuclei, and mitochondria. Conclusively, our study suggests that the complexation of organic contaminants with proteins might mitigate their toxicity by reducing cellular uptake.	●	●								-		B	C
219	ADME	Zhang, X.; Chen, L.; Fei, X. C.; Ma, Y. S.; Gao, H. W.	Binding of PFOS to serum albumin and DNA: Insight into the molecular toxicity of perfluorochemicals	2009	BMC Mol Biol. 2009 Feb 25;10:16. doi: 10.1186/1471-2199-10-16.	BACKGROUND: Health risk from exposure of perfluorochemicals (PFCs) to wildlife and human has been a subject of great interest for understanding their molecular mechanism of toxicity. Although much work has been done, the toxigenicity of PFCs remains largely unknown. In this work, the non-covalent interactions between perfluorooctane sulfonate (PFOS) and serum albumin (SA) and DNA were investigated under normal physiological conditions, aiming to elucidate the toxigenicity of PFCs.RESULTS: In equilibrium dialysis assay, the bindings of PFOS to SA correspond to the Langmuir isothermal model with two-step sequence model. The saturation binding number of PFOS was 45 per molecule of SA and 1 per three base-pairs of DNA, respectively. ITC results showed that all the interactions were spontaneous driven by entropy change. Static quenching of the fluorescence of SA was observed when interacting with PFOS, indicating PFOS bound Trp residue of SA. CD spectra of SA and DNA changed obviously in the presence of PFOS. At normal physiological conditions, 1.2 mmol/l PFOS reduces the binding ratio of Vitamin B2 to SA by more than 30%.CONCLUSION: The ion bond, van der Waals force and hydrophobic interaction contributed to PFOS binding to peptide chain of SA and to the groove bases of DNA duplex. The non-covalent interactions of PFOS with SA and DNA alter their secondary conformations, with the physiological function of SA to transport Vitamin B2 being inhibited consequently. This work provides a useful experimental method for further studying the toxigenicity of PFCs.	●	●		●						-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献ランク①	文献ランク②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
220	ADME	Buist, Susan C N; Klaassen, Curtis D	Rat and mouse differences in gender-predominant expression of organic anion transporter (OAT1-3; SLC22A6-9) mRNA levels	2004	Drug Metab Dispos. 2004 Jun;32(6):620-5. doi: 10.1124/dmd.32.6.620.	Organic anion transporters (Oats) mediate the initial step of active renal excretion, specifically substrate uptake into proximal tubule cells. Despite extensive characterization of rat Oats, mouse Oat expression patterns are virtually unknown. This study was designed to identify basal expression patterns of mouse Oat1 (Slc22a6), Oat2 (Slc22a7), and Oat3 (Slc22a8) mRNA, compare these patterns with those in rat, and characterize postnatal development of mouse Oat mRNA. Tissues were collected from adult male and female 129J and C57BL/6 mice, and male and female C57BL/6 mice 0 to 40 days of age. Oat mRNA levels were determined by branched DNA signal amplification. Mouse Oat1 mRNA was primarily expressed in kidney of both strains, with male predominance. Mouse Oat2 mRNA levels were highest in kidney of both strains without gender predominance. In both strains, Oat3 mRNA was highest in kidney, and liver expression was male-predominant. However, only 129J mice had higher Oat3 mRNA levels in female kidney than in male kidney. During postnatal development, both Oat1 and Oat2 mRNA levels began to rise after 25 days of age. Oat3 mRNA levels rose gradually from birth through 40 days of age. Oat2 mRNA increased 30-fold during the first 40 days, whereas Oat1 and Oat3 increased about 2-fold. The most notable species differences in Oat mRNA expression were a lack of Oat2 female predominance in mouse kidney and a less dramatic Oat3 male predominance in mouse liver. With the exception of a significant species difference in Oat2 expression, many similarities were found between rat and mouse Oat mRNA levels.				●							-		C	C
221	ADME	Burns, Darcy C; Ellis, David A; Li, Hongxia; McMurdo, Colin J; Webster, Eva	Experimental pKa determination for perfluorooctanoic acid (PFOA) and the potential impact of pKa concentration dependence on laboratory-measured phenomena and environmental modeling	2008	Environ Sci Technol. 2008 Dec 15;42(24):9283-8. doi: 10.1021/es802047v.	An accurately measured equilibrium acid dissociation constant (pKa) is essential for understanding and predicting the fate of perfluorocarboxylic acids (PFCAs) in the environment. The aqueous pKa of perfluorooctanoic acid (PFOA) has been determined potentiometrically using a standard water-methanol mixed solvent approach and was found to be 3.8 +/- 0.1. The acidity of PFOA is thus considerably weaker than its shorter-chain PFCA homologues. This was attributed to differences in molecular and electronic structure, coupled with solvation effects. The pKa of PFOA was suppressed to approximately 2.3 at higher concentrations because of the aggregation of perfluorooctanoate (PFO). Often, PFCA partion coefficients are determined at concentrations above those found in the environment. Thus, it was suggested that a pKa correction factor, which accounts for this concentration-dependent shift in acid/base equilibrium, should be applied to PFCA partition efficients before they are implemented in environmental fate models. A pKa of 3.8 +/- 0.1 suggests that a considerable concentration of the PFCA exists as the neutral species in the aqueous environment for example, in typical Ontario rainwater, it is approximately 17%. Transport, fate, and partitioning models have often ignored the presence this species completely. The environmental dissemination of PFCAs could, in part, be explained by considering the role of the neutral species.				●		●					-		B	C
222	ADME	Butenhoff, John L; Pieterman, Elsbeth; Ehresman, David J; Gorman, Gregory S; Olsen, Geary W; Chang, Shu-Ching; Princen, Hans M G	Distribution of perfluorooctanesulfonate and perfluorooctanoate into human plasma lipoprotein fractions	2012	Toxicol Lett. 2012 May 5;210(3):360-5. doi: 10.1016/j.toxlet.2012.02.013. Epub 2012 Feb 24.	Some cross-sectional epidemiological studies have reported positive associations of serum concentrations of non-high density lipoprotein cholesterol with serum perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA). However, the strength of the reported associations is inconsistent for exposure-response across three orders of magnitude of serum PFOS and/or PFOA concentrations. These positive associations are unexpected based on toxicological/mechanistic studies, suggesting that the associations may have a biological, rather than a causal, basis. This study tested the hypothesis that PFOS and PFOA distribute into serum lipoprotein fractions such that increases in serum lipoproteins would result in corresponding increases in serum concentrations of PFOS and PFOA. Based on observed binding of PFOS and PFOA to isolated β-lipoproteins in physiological saline (96% and 40% bound, respectively) in preliminary experiments using ultrafiltration and LC-MS/MS methods, binding to human donor plasma lipoprotein fractions was investigated by two density gradient methods. The majority of PFOS and PFOA recovered masses were found in lipoprotein-depleted plasma. Plasma density gradient fractionation data suggested that maximally 9% of PFOS distributes to lipoprotein-containing fractions, yet only 1% or less of PFOA is so distributed. These data do not support a strong role for plasma lipoprotein fractions in explaining the inconsistent dose-response associations reported in cross-sectional epidemiological studies.				●	●	●					-		B	B
223	ADME	Chang, Shu-Ching; Das, Kaberi; Ehresman, David J; Ellefson, Mark E; Gorman, Gregory S; Hart, Jill A; Noker, Patricia E; Tan, Yu-Mei; Lieder, Paul H; Lau, Christopher; Olsen, Geary W; Butenhoff, John L	Comparative pharmacokinetics of perfluorobutyrate (PFBA) in rats, mice, monkeys, and humans and relevance to human exposure via drinking water	2008	Toxicol Sci. 2008 Jul;104(1):40-53. doi: 10.1093/toxsci/kfn057. Epub 2008 Mar 18.	Perfluorobutyrate (PFBA) has been detected in precipitation, surface waters, water treatment effluent, and in public and private wells in Minnesota at up to low microg/l concentrations. We evaluated the pharmacokinetics of PFBA in rats, mice, monkeys, and humans to provide a rational basis for dose selection in toxicological studies and to aid in human-health-risk assessment. Studies included (1) rats--iv and oral; (2) mice--oral; (3) monkeys--iv; and (4) humans--occupationally exposed volunteers. PFBA was determined in serum (all species), liver (rats and mice), urine (rats, mice, and monkeys), and feces (rats and mice). In addition, we characterized serum PFBA concentrations in 177 individuals with potential exposure to PFBA through drinking water. Mean terminal serum PFBA elimination half-lives for males (M) and females (F), respectively, in h were (1) for rats given 30 mg/kg, 9.22 and 1.76 (oral), and 6.38 and 1.03 (iv); (2) for mice given oral doses of 10, 30, or 100 mg/kg ammonium PFBA, 13.34 and 2.87 at 10 mg/kg, 16.25 and 3.08 at 30 mg/kg; and 5.22 and 2.79 at 100 mg/kg; (3) for monkeys given 10 mg/kg iv, 40.32 and 41.04; and (4) for humans, 72.16 and 87.00 (74.63 combined). Volume of distribution estimates indicated primarily extracellular distribution. Among individuals with plausible exposure via drinking water, 96% of serum PFBA concentrations were < 2 ng/ml (maximum 6 ng/ml). These findings demonstrate that PFBA is eliminated efficiently from serum with a low potential for accumulation from repeated exposure.				●							-		C	C
224	ADME	Chengelis, Christopher P; Kirkpatrick, Jeannie B; Myers, Nichole R; Shinohara, Motoki; Stetson, Philip L; Sved, Daniel W	Comparison of the toxicokinetic behavior of perfluorohexanoic acid (PFHxA) and nonafluorobutane-1-sulfonic acid (PFBS) in Cynomolgus monkeys and rats	2009	Reprod Toxicol. 2009 Jun;27(3-4):400-406. doi: 10.1016/j.reprotox.2009.01.013. Epub 2009 Feb 11.	The toxicokinetics of perfluorohexanoic acid (PFHxA) and nonafluoro-1-butanesulfonic acid (PFBS) were evaluated in Sprague-Dawley rats and cynomolgus monkeys. Systemic exposure to PFHxA was lower than for PFBS following single equivalent intravenous or oral (rat only) doses. Serum clearance was more rapid for PFHxA than for PFBS. In rats, exposure to PFHxA and PFBS was up to 8-fold (intravenous) and 4-fold (oral) higher for males than females and serum clearance of PFHxA and PFBS was more rapid in females than males; however, there was no appreciable difference in the extent or rate of urinary elimination between compounds or genders. There were no apparent differences between genders in the serum half-life for PFHxA following 26 days of repeated oral dosing in rats; exposure decreased upon repeated dosing.				●							-		B	B
225	ADME	Clewell, H J 3rd; Andersen, M E	Risk assessment extrapolations and physiological modeling	1985	Toxicol Ind Health. 1985 Dec;1(4):111-31. doi: 10.1177/074823378500100408.	The process of assessing the risk associated with human exposure to environmental chemicals inevitably relies on a number of assumptions, estimates and rationalizations. One of the more challenging aspects of risk assessment involves the need to extrapolate beyond the range of conditions used in experimental animal studies to predict anticipated human risks. The most obvious extrapolation required is that from the tested animal species to humans; but others are also generally required, including extrapolating from high dose to low dose, from one route of exposure to another and from one exposure timeframe to another. Several avenues are available for attempting these extrapolations, ranging from the assumption of strict correspondence of dose to the use of statistical correlations. One promising alternative for conducting more scientifically sound extrapolations is that of using physiologically based pharmacokinetic models that contain sufficient biological detail to allow pharmacokinetic behavior to be predicted for widely different exposure scenarios. In recent years, successful physiological models have been developed for a variety of volatile and nonvolatile chemicals, and their ability to perform the extrapolations needed in risk assessment has been demonstrated. Techniques for determining the necessary biochemical parameters are readily available, and the computational requirements are now within the scope of even a personal computer. In addition to providing a sound framework for extrapolation, the predictive power of a physiologically based pharmacokinetic model makes it a useful tool for more reliable dose selection before beginning large-scale studies, as well as for the retrospective analysis of experimental results.				●							-		C	C
226	ADME	Goecke, C M; Jarnot, B M; Reo, N V	A comparative toxicological investigation of perfluorocarboxylic acids in rats by fluorine-19 NMR spectroscopy	1992	Chem Res Toxicol. 1992 Jul-Aug;5(4):512-9. doi: 10.1021/tx00028a009.	Male Fischer-344 rats administered a single intraperitoneal dose of perfluoro-n-octanoic acid (PFOA) or perfluoro-n-decanoic acid (PFDA) display a similar "wasting toxicity" characteristic of perfluorocarboxylic acids, with marked differences in temporal expression. Food/water consumption and urine output were monitored daily in PFOA-treated, PFDA-treated, and control rats. Fluorine-19 nuclear magnetic resonance (NMR) spectroscopy was used to monitor these fluorocarbons and possible fluoro metabolites in vivo, and to correlate differences in elimination with differences in effective toxicity. The data reveal a prolonged hypophagic response to PFDA and a more acute but transient response associated with PFOA treatment. PFOA causes a greater decline in food consumption than PFDA within the first 24 h postdose. PFOA-treated rats also show a ca. 2.5-fold increase in urine output on day 1, with only a slight increase in water consumption. In contrast to PFDA, PFOA-treated rats recover from hypophagia within 8 days. Fluorine-19 NMR spectra of various bodily fluids and liver in vivo display resonances of the parent PFOA or PFDA compounds and do not reveal any evidence of metabolism. Inorganic fluoride from dietary sources is detected in urine from both exposed and control rats. Differences in the route of excretion of PFOA vs PFDA are apparent from the spectral signal-to-noise ratio. The data suggest that PFOA is more readily excreted in the urine while PFDA is preferentially carried in bile. These apparent differences in elimination may account for their observed differences in effective toxicity. The acute transient toxicity and higher LD50 associated with PFOA may result from its rapid renal clearance.(ABSTRACT TRUNCATED AT 250 WORDS)				●							-		B	B
227	ADME	Han, Xing; Hinderliter, Paul M; Snow, Timothy A; Jepson, Gary W	Binding of perfluorooctanoic acid to rat liver-form and kidney-form α2u-globulins	2004	Drug Chem Toxicol. 2004 Nov;27(4):341-60. doi: 10.1081/dct-200039725.	Perfluorooctanoic acid (PFOA) is an organic fluorochemical and is reported to have a long half-life in human blood. Its urinary elimination in rats is markedly sex-dependent, and characterized by significantly longer plasma half-life of PFOA in male rats than in females. It has been postulated that male-specific PFOA binding protein(s) is responsible for the long half-life of PFOA in male rats. In this paper, two male rat specific proteins, liver- and kidney-form alpha2u-globulins (A2U(L) and A2U(K)), were purified from male rat urine and kidney, respectively. The binding of these two nroteins to PFOA was investigated using ligand blotting, electrospray ionization mass spectrometry and fluorescence competitive binding assay. The results revealed that both A2U(L) and A2U(K) were able to bind PFOA in vitro under physiological conditions, and that PFOA and a fluorescent-labeled fatty acid shared the same binding site on both A2U(L) and A2U(K). The binding affinities, however, are relatively weak. The estimated dissociation constants are in the 10(-3) M range, indicating that bindings of PFOA to either A2U(L) or A2U(K) cannot adequately explain the sex-dependent elimination of PFOA in rats, and it is unlikely that PFOA-A2U(K) binding would induce A2U nephropathy as seen with, for example, 1,4-dichlorobenzene.				●		●					-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報抽出対象	文献ランク①	文献ランク②
228	ADME	Han, Xing; Kemper, Raymond A; Jepson, Gary W	Subcellular distribution and protein binding of perfluorooctanoic acid in rat liver and kidney	2005	Drug Chem Toxicol. 2005;28(2):197-209. doi: 10.1081/dct-52547.	Perfluorooctanoic acid (PFOA) is an organic fluorochemical, and its elimination in rats is markedly sex-dependent. Liver and kidney are two primary tissues of distribution of PFOA in rats. In this study, the subcellular distribution of PFOA in male and female rat liver and kidney was examined. The results demonstrated that PFOA content in the liver cytosol of the female rat was significantly higher (49 +/- 6% of total radioactive residues, TRR) than in the male liver (26 +/- 5% TRR), whereas PFOA distribution in the heavier subcellular fractions, especially the nuclei and cell debris fraction, was marginally higher in male rat liver. In rat kidney, more than 70% of PFOA was distributed in the cytosolic fraction, with no significant difference between sexes. The degree of protein binding of PFOA in rat liver and kidney cytosol was analyzed by two different chromatographic methods. The percentage of protein-bound PFOA in the liver cytosol was found to be approximately 55% in both male and female rats. In contrast, significantly more PFOA was bound to cytosolic proteins in the kidney of male rats (42 +/- 6% TRR) than in females (17 +/- 5% TRR). Ligand blotting analysis revealed that multiple proteins from the liver cytosol, nuclei, and mitochondria fractions were capable of specific binding to PFOA.				●		●				-		B	B
229	ADME	Harris, Leona A; Barton, Hugh A	Comparing single and repeated dosimetry data for perfluorooctane sulfonate in rats	2008	Toxicol Lett. 2008 Oct 1;181(3):148-56. doi: 10.1016/j.toxlet.2008.07.014. Epub 2008 Jul 29.	Perfluorooctane sulfonate (PFOS) is a member of a class of perfluorinated chemicals used in a variety of consumer and industrial applications because of their oleophobic and hydrophobic properties. It has been shown to cause toxicity in adult and developing laboratory animals. Because PFOS has also been shown to be widely distributed throughout the environment, there have been concerns about its potential health risk to humans. Limited pharmacokinetic data for PFOS are available in rodents and humans, while epidemiological studies of workers and extensive toxicity studies in rodents have been performed. The existing pharmacokinetic and toxicity database in rodents can be useful in the cross-species extrapolations needed to evaluate and interpret internal dosimetry in humans. A mathematical model that describes the disposition of PFOS in adult rats following intravenous, oral, and chronic dietary exposures was developed to gain a better understanding of the pharmacokinetics of PFOS and to determine whether single-dose kinetics are predictive of repeated-dose kinetics. In order to characterize existing time-course data, time-dependent and concentration-dependent changes in the pharmacokinetic parameters for urinary and biliary clearance and liver distribution were needed. Whether these time-dependent changes represent inconsistencies across experiments, effects of aging in the rats, or chemically induced changes in pharmacokinetics remains to be determined.				●						-		B	B
230	ADME	Hsu, Vicky; de L T Vieira, Manuela; Zhao, Ping; Zhang, Lei; Zheng, Jenny Huimin; Nordmark, Anna; Berglund, Eva Gil; Giacomini, Kathleen M; Huang, Shiew-Mei	Towards quantitation of the effects of renal impairment and probenecid inhibition on kidney uptake and efflux transporters, using physiologically based pharmacokinetic modelling and simulations	2014	Clin Pharmacokinet. 2014 Mar;53(3):283-293. doi: 10.1007/s40262-013-0117-y.	BACKGROUND AND OBJECTIVES: The kidney is a major drug-eliminating organ. Renal impairment or concomitant use of transporter inhibitors may decrease active secretion and increase exposure to a drug that is a substrate of kidney secretory transporters. However, prediction of the effects of patient factors on kidney transporters remains challenging because of the multiplicity of transporters and the lack of understanding of their abundance and specificity. The objective of this study was to use physiologically based pharmacokinetic (PBPK) modelling to evaluate the effects of patient factors on kidney transporters. METHODS: Models for three renally cleared drugs (oseltamivir carboxylate, cidofovir and cefuroxime) were developed using a general PBPK platform, with the contributions of net basolateral uptake transport (T up,b) and apical efflux transport (T eff,a) being specifically defined. RESULTS AND CONCLUSION: We demonstrated the practical use of PBPK models to: (1) define transporter-mediated renal secretion, using plasma and urine data; (2) inform a change in the system-dependent parameter (≥10-fold reduction in the functional 'proximal tubule cells per gram kidney') in severe renal impairment that is responsible for the decreased secretory transport activities of test drugs; (3) derive an in vivo, plasma unbound inhibition constant of T up,b by probenecid (≤1 μM), based on observed drug interaction data; and (4) suggest a plausible mechanism of probenecid preferentially inhibiting T up,b in order to alleviate cidofovir-induced nephrotoxicity.				●						-		C	C
231	ADME	Igari, Y; Sugiyama, Y; Sawada, Y; Iga, T; Hanano, M	Prediction of diazepam disposition in the rat and man by a physiologically based pharmacokinetic model	1983	J Pharmacokinet Biopharm. 1983 Dec;11(6):577-93. doi: 10.1007/BF01059058.	A physiologically based pharmacokinetic model for diazepam disposition was developed in the rat, incorporating anatomical, physiological, and biochemical parameters, i.e., tissue volume, blood flow rate, serum free fraction, distribution of diazepam into red blood cells, drug metabolism and tissue-to-blood distribution ratio. The serum free fraction of diazepam was determined by equilibrium dialysis at 37 degrees C and was constant over a wide concentration range. Partition of diazepam between plasma and erythrocytes was determined in vitro at 37 degrees C, and the resultant blood-to-plasma concentration ratio was constant over a wide concentration range. The enzymatic parameters (Km, Vmax) of the eliminating organs, i.e., liver, kidney, and lung, previously determined using microsomes, were used for the prediction. The tissue-to-blood distribution ratios inferred by inspection of the data when pseudoequilibrium is reached after i.v. bolus injection of 1.2 mg/kg diazepam were corrected according to the method of Chen and Gross. Predicted diazepam concentration time-course profiles in plasma and various organs or tissues, using an 11-compartmental model, were compared with those observed. Prediction was successful in all compartments including brain, the target organ of diazepam. Scale-up of the disposition kinetics of diazepam from rat to man was also successful.				●						-		C	C
232	ADME	Jandacek, R J; Rider, T; Keller, E R; Tso, P	The effect of olestra on the absorption, excretion and storage of 2,2',5,5' tetrachlorobiphenyl; 3,3',4,4' tetrachlorobiphenyl; and perfluorooctanoic acid	2010	Environ Int. 2010 Nov;36(8):880-3. doi: 10.1016/j.envint.2009.06.010. Epub 2009 Jul 17.	Mice were gavaged with either (14)C-labeled 2,2'5,5' tetrachlorobiphenyl; 3,3',4,4' tetrachlorobiphenyl; or perfluorooctanoic acid. Absorption of these compounds was determined by assay of feces collected for 48 h after the gavage. Part of the animals received test diets containing olestra during this 48-hour period to determine its effect on absorption of the compounds. Mice that received the diet without olestra during this period were divided into groups that either continued the diet without olestra or changed to a diet containing olestra. These diets were continued for 7 days, and a second 48-hour fecal collection was made to measure the effect of olestra on enterohepatic circulation of the compounds and their metabolites. The animals were sacrificed, and blood, fat, and liver concentrations of (14)C were measured. Olestra decreased the absorption of 2,2',5,5' tetrachlorobiphenyl. It also reduced tissue and blood concentrations of this compound. Olestra also decreased the absorption of 3,3',4,4' tetrachlorobiphenyl, but it did not alter enterohepatic circulation or tissue concentrations. Olestra significantly increased the excretion of perfluorooctanoic acid in the second 48-hour collection, suggesting an effect on enterohepatic circulation. It did not, however, alter tissue concentrations of perfluorooctanoic acid. These data are consistent with previously observed effects of olestra on the absorption and storage of lipophilic compounds.				●						-		B	C
233	ADME	Jensen, Morten Søndergaard; Nørgaard-Pedersen, Bent; Toft, Gunnar; Hougaard, David M; Bonde, Jens Peter; Cohen, Arieh; Thulstrup, Ane Marie; Ivell, Richard; Anand-Ivell, Ravinder; Lindh, Christian H; Jönsson, Bo A G	Phthalates and perfluorooctanesulfonic acid in human amniotic fluid: Temporal trends and timing of amniocentesis in pregnancy	2012	Environ Health Perspect. 2012 Jun;120(6):897-903. doi: 10.1289/ehp.1104522. Epub 2012 Mar 7.	BACKGROUND: Measures of prenatal environmental exposures are important, and amniotic fluid levels may directly reflect fetal exposures during hypothesized windows of vulnerability. OBJECTIVES: We aimed to detect various phthalate metabolites and perfluorooctanesulfonic acid (PFOS) in human amniotic fluid, to study temporal exposure trends, and to estimate potential associations with gestational week of amniocentesis and maternal age and parity at amniocentesis. METHODS: We studied 300 randomly selected second-trimester amniotic fluid samples from a Danish pregnancy-screening biobank covering 1980 through 1996. We used only samples from male offspring pregnancies. We assayed the environmental pollutants by liquid chromatography/triple quadrupole mass spectrometry and analyzed data using generalized linear regression models. RESULTS: We detected the di(2-ethylhexyl) phthalate (DEHP) metabolite mono(2-ethyl-5-carboxypentyl) phthalate (5cx-MEPP) at a median concentration of 0.27 ng/mL [interquartile range (IQR): 0.20-0.37 ng/mL], the diisononyl phthalate (DiNP) metabolite mono(4-methyl-7-carboxyheptyl) phthalate (7cx-MMeHP) at 0.07 ng/mL (IQR: 0.05-0.11 ng/mL), and PFOS at 1.1 ng/mL (IQR: 0.66-1.60 ng/mL). An increase of 1 calendar year was associated with 3.5% lower [95% confidence interval (CI): -4.8%, -2.1%] 5cx-MEPP levels and with 7.1% higher (95% CI: 5.3%, 9.0%) 7cx-MMeHP levels. For each later gestational week of amniocentesis, 5cx-MEPP was 9.9% higher (95% CI: 4.8%, 15.2%), 7cx-MMeHP was 8.6% higher (95: CI: 2.7%, 14.9%), and PFOS was 9.4% higher (95: CI: 3.3%, 15.9%). We observed no associations with maternal age or parity. CONCLUSIONS: Measured metabolite levels appeared to parallel decreasing DEHP exposure and increasing DiNP exposure during the study period. The environmental pollutant levels were positively associated with later gestational age at amniocentesis during pregnancy weeks 12-22.				●						-		B	B
234	ADME	Johnson JD.	Final report. Analytical study, single-dose dermal absorption/toxicity study of T6049 in rabbits	1995	In vivo reference number: HWI#6329-130. 3M. SCD Division.	No abstract available				●						企業データ		D	D
235	ADME	Johnson JD.	Final report. Analytical study, single-dose dermal absorption/toxicity study of T6053 in rabbits (lithium perfluorooctane sulfonate)	1995	In vivo study reference number: HWI#6329-137. 3M. SCD Division	No abstract available				●						企業データ		D	D
236	ADME	Johnson JD, Ober RE.	Extent and route of excretion and tissue distribution of total carbon-14 in rats after a single intravenous dose of FC-95-14C	1980	3M. Submitted to the U.S. Environmental Protection Agency's Administrative Record. AR226-0006.	No abstract available				●						企業データ		D	D
237	ADME	Johnson JD, Ober RE.	Absorption of FC-143-14C in rats after a single oral dose	1999	In: Exploratory 28-day oral toxicity study with telomer alcohol, telomer acrylate, PFHS, and PFOS (POS control) by daily gavage in the rat, w/CVR LTR DTD, 051500 (Sanitized). 3M. Submitted to the U.S. Environmental Protection Agency under TSCA Section FYI. OTS05001378S.	No abstract available				●						企業データ		D	D
238	ADME	Johnson JD, Ober RE.	Extent and route of excretion and tissue distribution of total carbon-14 in male and female rats after a single IV dose of FC-143-14C	1999	In: Exploratory 28-day oral toxicity study with telomer alcohol, telomer acrylate, PFHS, and PFOS (POS control) by daily gavage in the rat, w/CVR letter dated, 051500 (Sanitized). 3M. Submitted to the U.S. Environmental Protection Agency under TSCA Section FYI. OTS05001378S.	No abstract available				●						企業データ		D	D

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
239	ADME	Katakura, M.; Kudo, N.; Tsuda, T.; Hibino, Y.; Mitsumoto, A.; Kawashima, Y.	Rat organic anion transporter 3 and organic anion transporting polypeptide 1 mediate perfluorooctanoic acid transport	2007	Journal of Health Science, 53(1) pp 77–83 (2007), doi: 10.1248/jhs.53.77	The mechanism by which perfluorooctanoic acid (PFOA) is transported in the kidney was studied in rats. We hypothesized that some transporters that are expressed in the basolateral and/or brush border membrane of proximal tubular cells mediate the transport of PFOA. Mannitol infusion, which caused an increase in the urine flow rate, significantly increased the renal clearance (CLR) of PFOA in both male and female rats. Feeding a low-phosphate diet that causes an increase in the expression of rat type II sodium-dependent phosphate transporter (Npt2) reduced the CLR in both male and female rats. These suggest that PFOA is reabsorbed in the proximal tubules, and that a phosphate transporter may be responsible for the renal transport of PFOA. The CLR of PFOA in Eisai hyperbilirubinemic rats that lack multidrug resistance-associated protein 2 (MRP2) was not different from that of the wild type, suggesting that MRP2 is not responsible for the renal transport of PFOA. Three candidate transporters, organic anion-tran sporting polypeptide 1 (oatp1), Npt2, and organic anion transporter 3 (OAT3) were studied to clarify whether these transporters facilitate [C-14]PFOA transport in functional studies in Xenopus laevis oocytes. Both oatp1 and OAT3 facilitated [C-14] PFOA transport while Npt2 did not. These results　suggest that both oatp1 and OAT3 mediate, at least in part, the transport of PFOA in the proximal tubules of rat kidney.				●						-		B	B
240	ADME	Kemper, Raymond A; Nabb, Diane L	In vitro studies in microsomes from rat and human liver, kidney, and intestine suggest that perfluorooctanoic acid is not a substrate for microsomal UDP-glucuronosyltransferases	2005	Drug Chem Toxicol. 2005;28(3):281-7. doi: 10.1081/dct-200064468.	Perfluorooctanoic acid (PFOA) is a fluorinated fatty acid analogue used as a surfactant in the manufacture of fluoropolymers. Previous studies have indicated that PFOA was metabolically inert in mammals, but recent metabolism studies with related fluorochemicals suggested that PFOA might form a glucuronide conjugate. [(14)C(1)]-PFOA was incubated with male and female human and rat liver, kidney, and small intestine microsomes. Incubations were carried out in the presence of alamethicin and beta-saccharolactone to increase access of PFOA to the enzyme active site and to inhibit potential hydrolysis of PFOA-glucuronide by microsomal beta-glucuronidase, respectively. Although positive control experiments using p-nitrophenol demonstrated significant UDP-glucuronosyltransferase (UDPGT) activity in all of the tested microsomal preparations, no evidence for formation of a PFOA-glucuronide was obtained, either by high-sensitivity radiochromatography or by LC/MS. These data suggest that PFOA is not a substrate for human or rodent microsomal UDPGTs.				●	●	●				-		B	B
241	ADME	Kobayashi, Yasuna; Hirokawa, Noriko; Ohshiro, Naomi; Sekine, Takashi; Sasaki, Tadanori; Tokuyama, Shogo; Endou, Hitoshi; Yamamoto, Toshinori	Differential gene expression of organic anion transporters in male and female rats	2002	Biochem Biophys Res Commun. 2002 Jan 11;290(1):482-7. doi: 10.1006/bbrc.2001.6180.	Sex-related differential gene expression of organic anion transporters (rOAT1, rOAT2, and rOAT3) in rat brain, liver, and kidney was investigated. There were no sex differences in the expression of rOAT1 mRNA. rOAT2 mRNA was abundant in the liver and weakly expressed in the kidney of male rats; however, the OAT2 gene was strongly expressed in both organs of females. The abundance of rOAT2 mRNA markedly increased in castrated male rat kidney; however, treatment of castrated male rats with testosterone led to a decrease of rOAT2 mRNA. Expression of rOAT3 mRNA in intact female rats was found in the kidney and brain, whereas in males rOAT3 mRNA was also found in the liver. rOAT3 mRNA markedly decreased in the liver of castrated male rats but increased in testosterone-treated castrated male rats. Moreover, rOAT3 mRNA increased in the hypophysectomized female rat liver, indicating that rOAT3 is an inducible isoform. The present findings suggest that sex steroids play an important role in the expression and maintenance of OAT2/3 isoforms in the rat liver and kidney. Our results provide information on the differential gene expression of OAT isoforms with sex hormone dependency.				●						-		C	C
242	ADME	Kudo, Naomi; Sakai, Ayako; Mitsumoto, Atsushi; Hibino, Yasuhide; Tsuda, Tadashi; Kawashima, Yoichi	Tissue distribution and hepatic subcellular distribution of perfluorooctanoic acid at low dose are different from those at high dose in rats	2007	Biol Pharm Bull. 2007 Aug;30(8):1535-40. doi: 10.1248/bpb.30.1535.	Fate of perfluorooctanoic acid (PFOA) after an intravenous injection to male rats at the dose of 0.041 mg/kg body weight was compared with that at the dose of 16.56 mg/kg body weight. In the liver, 52% and 27% of PFOA dosed was recovered 2 h after an intravenous injection at the low and the high doses, respectively. By contrast, larger proportion of PFOA dosed was distributed to serum, other tissues and carcass at the high dose compared with the low dose. Subcellular distribution of PFOA was determined in the liver. At the dose of 0.041 mg/kg, 45%, 34%, 18% and 3% were distributed to 8000 g pellet, 18000g pellet, 105000g pellet and 105000g supernatant fraction, respectively; 28%, 17%, 13% and 43% of PFOA were distributed to these fractions, respectively, at the dose of 16.56 mg/kg. The higher the concentration of hepatic PFOA was, the more the PFOA was distributed to 105000g supernatant fraction. Biliary excretion index increased as PFOA concentration raised in the liver. These results suggest that PFOA is preferentially taken-up by the liver, and distributed to membrane fractions, especially 18000g pellet, and hardly excreted into bile when exposed at very low dose.				●		●				-		B	B
243	ADME	Li, Ning; Hartley, Dylan P; Cherrington, Nathan J; Klaassen, Curtis D	Tissue expression, ontogeny, and inducibility of rat organic anion transporting polypeptide	2002	J Pharmacol Exp Ther. 2002 May;301(2):551-60. doi: 10.1124/jpet.301.2.551.	To date, organic anion transporting polypeptide 4 (Oatp4; Slc21a10) is known as a liver-specific and sodium-independent transporter that mediates transport of a variety of compounds. The purpose of this study was to determine whether Oatp4 mRNA expression is specific to the liver compared with Oatp1, 2, 3, or 5. In addition, the effect of gender and age was determined by assessing the expression of Oatp4 mRNA during the postnatal development of rats. Furthermore, to determine whether Oatp4 gene expression is coordinately modulated by drug-metabolizing enzyme inducers, male rats were administered chemicals known to induce the expression of drug-metabolizing enzymes through six mechanisms: the aryl hydrocarbon receptor, constitutive androstane receptor, pregnane X receptor, peroxisome proliferator-activated receptor, electrophile response element, or CYP2E1 inducers. The levels of Oatp1, 2, 3, 4, and 5 mRNA were measured using the branched DNA signal amplification technique. The tissue distribution of Oatp4 was almost exclusively expressed in liver in contrast to Oatp1, 2, 3, and 5. The hepatic expression of Oatp4 was low in newborn rats and increased gradually to the adult level with no significant difference between genders. The expression of Oatp4 was not consistently induced by any of the six groups of enzyme inducers. These findings continue to suggest that Oatp4 is expressed specifically in the liver. The preference of Oatp4 for endogenous compounds coupled with its refractory response to known drug-metabolizing enzyme inducers suggests that Oatp4 may be largely responsible for the homeostasis of endogenous rather than				●						-		C	C
244	ADME	Lien, Guang-Wen; Huang, Ching-Chun; Wu, Kuen-Yuh; Chen, Mei-Huei; Lin, Chien-Yu; Chen, Chia-Yang; Hsieh, Wu-Shiun; Chen, Pau-Chung	Neonatal-maternal factors and perfluoroalkyl substances in cord blood	2013	Chemosphere. 2013 Aug;92(7):843-50. doi: 10.1016/j.chemosphere.2013.04.038. Epub 2013 May 18.	Perfluoroalkyl substances (PFASs) can cross the placenta, enter fetal circulation, and were found to correlate with adverse fetal growth. However, determinants of cord blood PFASs are not fully characterized. The study aimed to explore the association between PFASs and neonatal-maternal factors within a Taiwanese birth cohort. We selected subjects from Taiwan Birth Panel Study, which enrolled 486 infant-mother pairs in 2004-2005. We collected cord blood and analyzed perfluorooctanoic acid (PFOA), perfluorooctanyl sulfonate (PFOS), perfluorononanoic acid (PFNA) and perfluoroundecanoic acid (PFUA) using a simple protein precipitation and an ultra-high performance liquid chromatography/tandem mass spectrometry. We retrieved information pertaining to maternal socio-demographics, lifestyle- and dietary-related factors through structured questionnaires during the postpartum hospital stay. A total of 439 subjects, with 90% response rate, have completed serum analysis and questionnaire survey. The median concentrations for PFOA, PFOS, PFNA, and PFUA in cord blood were 1.86, 5.67, 3.00, and 13.5ngmL(-1), respectively. After adjusting for potential confounders, multiple linear regression models revealed that log10-PFOA was positively associated with maternal age (β=0.011) and negatively associated with multiparity (β=-0.044). Log10-PFOS was negatively correlated with birth weight (β=-0.011) and higher maternal education (senior high school: β=-0.067; university: β=-0.088). Log10-PFUA tended to negatively associate with gender, male infants (β=-0.075), and using cosmetics during pregnancy (β=-0.065).Interestingly, presence of cockroaches in the home was positively associated with log10-PFOA (β=0.041) and 1og10-PFNA (β=0.123). In conclusion, this study demonstrated several factors to correlate with cord blood PFASs and further investigation are still needed for confirmation of exposure routes.				●						-		B	B
245	ADME	Lu, R.; Kanai, N.; Bao, Y.; Wolkoff, A. W.; Schuster, V. L.	Regulation of renal oatp mRNA expression by testosterone	1996	Am J Physiol. 1996 Feb;270(2 Pt 2):F332-7. doi: 10.1152/ajprenal.1996.270.2.F332.	A recently cloned cDNA encodes the so-called "organic anion-transporting polypeptide" (i.e., oatp), which is expressed in rat liver and in the kidney S3 proximal tubule. functional characterization of the cloned transporter indicates that estradiol 17 beta-D-glucuronide is a major substrate. Because the urinary excretion of glucuronidated steroids differs between males and females, we hypothesized that renal oatp expression may be under sex hormone control. Total RNA was isolated from male or female kidneys and probed with a digoxigenin-labeled oatp antisense riboprobe. Expression of oatp mRNA expression was quantitated by densitometry from Northern blots. Male kidneys expressed at least six distinct oatp transcripts (approximately 4.0, 3.2, 2.9, 2.6, 1.7, and 1.2 kb). Of these, the 3.2-kb band was consistently the strongest. In female rats, renal oatp mRNA expression was markedly less, such that only the 3.2-kb band was consistently detectable. Administering testosterone to female rats increased, and administering estradiol (E2) to male rats decreased, the steady-state levels of renal oatp mRNA. Gonadectomized male and female rats, as well as adrenalectomized male rats, were given pharmacological hormone replacement (testosterone, E2, or dexamethasone, respectively) by subcutaneous osmotic minipump. Castration of male rats produced a dramatic drop in the steady-state level of all six renal oatp transcripts. These were returned to normal by testosterone replacement. In contrast, there was no regulation of hepatic oatp mRNA expression by testosterone. Renal oatp mRNA expression in female rats was mildly increased by oophorectomy. Administration of E2 to oophorectomized females moderately suppressed renal oatp mRNA expression. Adrenalectomy produced a small decrease in oatp expression, but dexamethasone replacement failed to return expression to normal. We conclude that renal oatp mRNA expression is under strong (stimulatory) testosterone control and perhaps weaker (inhibitory) estrogen control. We speculate that this regulation of renal oatp expression is important in modulating the renal tubular secretion of conjugated E2.				●						-		C	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①C	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
246	ADME	Ljubojevic, Marija; Herak-Kramberger, Carol M; Hagos, Yohannes; Bahn, Andrew; Endou, Hitoshi; Burckhardt, Gerhard; Sabolic, Ivan	Rat renal cortical OAT1 and OAT3 exhibit gender differences determined by both androgen stimulation and estrogen inhibition	2004	Am J Physiol Renal Physiol. 2004 Jul;287(1):F124-38. doi: 10.1152/ajprenal.00029.2004. Epub 2004 Mar 9.	In rats, the secretion of p-aminohippurate (PAH) by the kidney is higher in males (M) than in females (F). The role of the major renal PAH transporters, OAT1 and OAT3, in the generation of these gender differences, as well as the responsible hormones and mechanisms, has not been clarified. Here we used various immunocytochemical methods to study effects of gender, gonadectomy, and treatment with sex hormones on localization and abundance of OAT1 and OAT3 along the rat nephron. Both transporters were localized to the basolateral membrane: OAT1 was strong in proximal tubule S2 and weak in the S3 segments, whereas OAT3 was stained in proximal tubule S1 and S2 segments, thick ascending limb, distal tubule, and in principal cells along the collecting duct. Gender differences in the expression of both transporters in adult rats (M > F) were observed only in the cortical tubules. OAT1 in the cortex was strongly reduced by castration in adult M, whereas the treatment of castrated M with testosterone, estradiol, or progesterone resulted in its complete restitution, further depression, or partial restitution, respectively. In adult F, ovariectomy weakly increased, whereas estradiol treatment of ovariectomized F strongly decreased, the expression of OAT1. The expression of OAT3 in the M and F cortex largely followed a similar pattern, except that ovariectomy and progesterone treatment showed no effect, whereas in other tissue zones gender differences were not observed. In prepubertal rats, the expression of OAT1 and OAT3 in the kidney cortex was low and showed no gender differences. Our data indicate that gender differences in the rat renal cortical OAT1 and OAT3 (M > F) appear after puberty and are determined by both a stimulatory effect of androgens (and progesterone in the case of OAT1) and an inhibitory effect of estrogens.				●						-		C	C
247	ADME	Luo, Zhipu; Shi, Xiaoli; Hu, Qin; Zhao, Bin; Huang, Mingdong	Structural evidence of perfluorooctane sulfonate transport by human serum albumin	2012	Chem Res Toxicol. 2012 May 21;25(5):990-2. doi: 10.1021/tx300112p. Epub 2012 Apr 16.	Perfluorooctane sulfonate (PFOS) is a man-made fluorosurfactant and globally persistent organic pollutant. PFOS is mainly distributed in blood with a long half-life for elimination. PFOS was found mainly bound to human serum albumin (HSA) in plasma, the most abundant protein in human blood plasma, which transports a variety of endogenous and exogenous ligands. However, the structural basis of such binding remains unclear. Here, we report the crystal structure of the HSA-PFOS complex and show that PFOS binds to HSA at a molar ratio of 2:1. In addition, PFOS binding renders the HSA structure more compact. Our results provide a structural mechanism to understand the retention of surfactants in human serum.				●						-		B	B
248	ADME	Maestri, Luciano; Negri, Sara; Ferrari, Massimo; Ghittori, Sergio; Fabris, Francesca; Danesino, Paolo; Imbriani, Marcello	Determination of perfluorooctanoic acid and perfluorooctanesulfonate in human tissues by liquid chromatography/single quadrupole mass spectrometry	2006	Rapid Commun Mass Spectrom. 2006;20(18):2728-34. doi: 10.1002/rcm.2661.	A method is described that permits the measurement of the levels of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) in human liver, kidney, adipose tissue, brain, basal ganglia, hypophysis, thyroid, gonads, pancreas, lung, skeletal muscle and blood, even in subjects not occupationally exposed to these compounds. The purification of samples involved the use of trifunctional (tC18) and strong anion-exchange (SAX) solid-phase extraction cartridges, and the analysis utilized a high-performance liquid chromatograph coupled to a single quadrupole mass spectrometer (LC/MS). The analyses were conducted on a mixed-bed reversed-phase column by gradient runs using 3 mM ammonium acetate/methanol mixtures at different proportions as the mobile phase. The detector was used in electrospray negative ion mode by recording simultaneously the ions m/z 413.0 (PFOA) and 499.0 (PFOS). Perfluorononanoic acid (PFNA), added to the samples before the purification, was used as the internal standard (ion monitored = m/z 463.6). The recovery rates of the extraction procedure ranged from 79.6 to 95.6% (CV% 1.7-7.4%) for PFOA, from 79.7 to 100.8% (CV% = 1.2-7.1) for PFOS, and from 89.1 to 102.3% (CV% = 0.9-5.2 %) for PFNA. The calibration curves were linear up to at least 400 ng of analytes per gram of tissue. The detection limits (signal-to-noise ratio = 3) were 0.1 ng/g for both PFOA and PFOS measured in all tissues except adipose tissue, where the limits were about 0.2 ng/g. The content of analytes in tissues varied from 0.3 to 3.8 ng/g (respectively: basal ganglia and lung) for PFOA, and from 1.0 to 13.6 ng/g (respectively: skeletal muscle and liver) for the linear isomer of PFOS. The method is suitable to evaluate the content of PFOA and PFOS in different tissues taken from the general population exposed to very low concentrations of these pollutants.				●	●					-		B	B
249	ADME	Maloney, E K; Waxman, D J	trans-Activation of PPARα and PPARγ by structurally diverse environmental chemicals	1999	Toxicol Appl Pharmacol. 1999 Dec 1;161(2):209-18. doi: 10.1006/taap.1999.8809.	A large number of industrial chemicals and environmental pollutants, including trichloroethylene (TCE), di(2-ethylhexyl)phthalate (DEHP), perfluorooctanoic acid (PFOA), and various phenoxyacetic acid herbicides, are nongenotoxic rodent hepatocarcinogens whose human health risk is uncertain. Rodent model studies have identified the receptor involved in the hepatotoxic and hepatocarcinogenic actions of these chemicals as peroxisome proliferator-activated receptor alpha (PPARalpha), a nuclear receptor that is highly expressed in liver. Humans exhibit a weak response to these peroxisome proliferator chemicals, which in part results from the relatively low level of PPARalpha expression in human liver. Cell transfection studies were carried out to investigate the interactions of peroxisome proliferator chemicals with PPARalpha, cloned from human and mouse, and with PPARgamma, a PPAR isoform that is highly expressed in multiple human tissues and is an important regulator of physiological processes such as adipogenesis and hematopoiesis. With three environmental chemicals, TCE, perchloroethylene, and DEHP, PPARalpha was found to be activated by metabolites, but not by the parent chemical. A decreased sensitivity of human PPARalpha compared to mouse PPARalpha to trans-activation was observed with some (Wy-14, 643, PFOA), but not other, peroxisome proliferators (TCE metabolites, trichloroacetate and dichloroacetate; and DEHP metabolites, mono[2-ethylhexyl]phthalate and 2-ethylhexanoic acid). Investigation of human and mouse PPARgamma revealed the transcriptional activity of this receptor to be stimulated by mono(2-ethylhexyl)phthalate, a DEHP metabolite that induces developmental and reproductive organ toxicities in rodents. This finding suggests that PPARgamma, which is highly expressed in human adipose tissue, where many lipophilic foreign chemicals tend to accumulate, as well as in colon, heart, liver, testis, spleen, and hematopoietic cells, may be a heretofore unrecognized target in human cells for a subset of industrial and environmental chemicals of the peroxisome proliferator class.				●						-		B	C
250	ADME	Mondal, Debapriya; Lopez-Espinosa, Maria-Jose; Armstrong, Ben; Stein, Cheryl R; Fletcher, Tony	Relationships of perfluorooctanoate and perfluorooctane sulfonate serum concentrations between mother-child pairs in a population with perfluorooctanoate exposure from drinking water	2012	Environ Health Perspect. 2012 May;120(5):752-7. doi: 10.1289/ehp.1104538. Epub 2012 Jan 23.	BACKGROUND: There are limited data on the associations between maternal or newborn and child exposure to perfluoroalkyl acids (PFAAs), including perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS). This study provides an opportunity to assess the association between PFAA concentrations in mother-child pairs in a population exposed to PFOA via drinking water. OBJECTIVES: We aimed to determine the relationship between mother-child PFAA serum concentrations and to examine how the child:mother ratio varies with child's age, child's sex, drinking-water PFOA concentration, reported bottled water use, and mother's breast-feeding intention. METHODS: We studied 4,943 mother-child pairs (children, 1-19 years of age). The child:mother PFAA ratio was stratified by possible determinants. Results are summarized as geometric mean ratios and correlation coefficients between mother-child pairs, overall and within strata. RESULTS: Child and mother PFOA and PFOS concentrations were correlated (r = 0.82 and 0.26, respectively). Up to about 12 years of age, children had higher serum PFOA concentrations than did their mothers. The highest child:mother PFOA ratio was found among children ≤ 5 years (44% higher than their mothers), which we attribute to in utero exposure and to exposure via breast milk and drinking water. Higher PFOS concentrations in children persisted until at least 19 years of age (42% higher than their mothers). Boys > 5 years of age had significantly higher PFOA and PFOS child:mother ratios than did girls. CONCLUSION: Concentrations of both PFOA and PFOS tended to be higher in children than in their mothers. This difference persisted until they were about 12 years of age for PFOA and at least 19 years of age for PFOS.				●	●	●				-	1	A	A
251	ADME	Morello-Frosch, Rachel; Cushing, Lara J; Jesdale, Bill M; Schwartz, Jackie M; Guo, Weihong; Guo, Tan; Wang, Miaomiao; Harwani, Suhash; Petropoulou, Syrago-Styliani E; Duong, Wendy; Park, June-Soo; Petreas, Myrto; Gajek, Ryszard; Alvaran, Josephine; She, Jianwen; Dobraca, Dina; Das, Rupali; Woodruff, Tracey J	Environmental chemicals in an urban population of pregnant women and their newborns from San Francisco	2016	Environ Sci Technol. 2016 Nov 15;50(22):12464-12472. doi: 10.1021/acs.est.6b03492. Epub 2016 Oct 26.	Exposures to environmental pollutants in utero may increase the risk of adverse health effects. We measured the concentrations of 59 potentially harmful chemicals in 77 maternal and 65 paired umbilical cord blood samples collected in San Francisco during 2010-2011, including polychlorinated biphenyls (PCBs), organochlorine pesticides (OCPs), polybrominated diphenyl ethers (PBDEs), hydroxylated PBDEs (OH-PBDEs), and perfluorinated compounds (PFCs) in serum and metals in whole blood. Consistent with previous studies, we found evidence that concentrations of mercury (Hg) and lower-brominated PBDEs were often higher in umbilical cord blood or serum than in maternal samples (median cord:maternal ratio > 1), while for most PFCs and lead (Pb), concentrations in cord blood or serum were generally equal to or lower than their maternal pair (median cord:maternal ratio ≤ 1). In contrast to the conclusions of a recent review, we found evidence that several PCBs and OCPs were also often higher in cord than maternal serum (median cord:maternal ratio > 1) when concentrations are assessed on a lipid-adjusted basis. Our findings suggest that for many chemicals, fetuses may experience higher exposures than their mothers and highlight the need to characterize potential health risks and inform policies aimed at reducing sources of exposure.				●						-		B	B
252	ADME	NAS/NRC.	Report of the oversight committee. In: Biologic markers in reproductive toxicology.	1989	In: Biologic markers in reproductive toxicology. Washington, DC: National Academy of Sciences, National Research Council, National Academy Press, 15-35.	No abstract available				●						NAS/NRC文書		D	D

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報対象抽出	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
253	ADME	Olsen, Geary W; Chang, Shu-Ching; Noker, Patricia E; Gorman, Gregory S; Ehresman, David J; Lieder, Paul H; Butenhoff, John L	A comparison of the pharmacokinetics of perfluorobutanesulfonate (PFBS) in rats, monkeys, and humans	2009	Toxicology. 2009 Feb 4;256(1-2):65-74. doi: 10.1016/j.tox.2008.11.008. Epub 2008 Nov 19.	Materials derived from perfluorobutanesulfonyl fluoride (PBSF, C(4)F(9)SO(2)F) have been introduced as replacements for eight-carbon homolog products that were manufactured from perfluorooctanesulfonyl fluoride (POSF, C(8)F(17)SO(2)F). Perfluorobutanesulfonate (PFBS, C(4)F(9)SO(3)(-)) is a surfactant and potential degradation product of PBSF-derived materials. The purpose of this series of studies was to evaluate the pharmacokinetics of PFBS in rats, monkeys, and humans, thereby providing critical information for human health risk assessment. Studies included: (1) intravenous (i.v.) elimination studies in rats and monkeys; (2) oral uptake and elimination studies in rats; and (3) human serum PFBS elimination in a group of workers with occupational exposure to potassium PFBS (K(+)PFBS). PFBS concentrations were determined in serum (all species), liver (rats), urine (all species), and feces (rats). In rats, the mean terminal serum PFBS elimination half-lives, after i.v. administration of 30mg/kg PFBS, were: males 4.51+/-2.22h (standard error) and females 3.96+/-0.21h. In monkeys, the mean terminal serum PFBS elimination half-lives, after i.v. administration of 10mg/kg PFBS, were: males 95.2+/-27.1h and females 83.2+/-41.9h. Although terminal serum half-lives in male and female rats were similar, without statistical significance, clearance (CL) was significantly greater in female rats (469+/-40mL/h) than male rats (119+/-34mL/h) with the area under the curve (AUC) significantly larger in male rats (294+/-77microg.h/mL) than female rats (65+/-5microg.h/mL). These differences were not observed in male and female monkeys. Volume of distribution estimates suggested distribution was primarily extracellular in both rats and monkeys, regardless of sex, and urine appeared to be a major route of elimination. Among 6 human subjects (5 male, 1 female) followed up to 180 days, the geometric mean serum elimination half-life for PFBS was 25.8 days (95% confidence interval 16.6-40.2). Urine was observed to be a pathway of elimination in the human. Although species-specific differences exist, these findings demonstrate that PFBS is eliminated at a greater rate from human serum than the higher chain homologs of perfluorooctanesulfonate (PFOS) and perfluorohexanesulfonate (PFHxS). Thus, compared to PFOS and PFHxS, PFBS has a much lower potential for accumulation in human serum after repeated occupational, non-occupational (e.g., consumer), or environmental exposures.				●						-		B	C
254	ADME	Salvalaglio, Matteo; Muscionico, Isabella; Cavallotti, Carlo	Determination of energies and sites of binding of PFOA and PFOS to human serum albumin	2010	J Phys Chem B. 2010 Nov 25;114(46):14860-74. doi: 10.1021/jp106584b. Epub 2010 Oct 28.	Structure and energies of the binding sites of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) to human serum albumin (HSA) were determined through molecular modeling. The calculations consisted of a compound approach based on docking, followed by molecular dynamics simulations and by the estimation of the free binding energies adopting WHAM-umbrella sampling and semiempirical methodologies. The binding sites so determined are common either to known HSA fatty acids sites or to other HSA sites known to bind to pharmaceutical compounds such as warfarin, thyroxine, indole, and benzodiazepin. Among the PFOA binding sites, five have interaction energies in excess of -6 kcal/mol, which become nine for PFOS. The calculated binding free energy of PFOA to the Trp 214 binding site is the highest among the PFOA complexes, -8.0 kcal/mol, in good agreement with literature experimental data. The PFOS binding site with the highest energy, -8.8 kcal/mol, is located near the Trp 214 binding site, thus partially affecting its activity. The maximum number of ligands that can be bound to HSA is 9 for PFOA and 11 for PFOS. The calculated data were adopted to predict the level of complexation of HSA as a function of the concentration of PFOA and PFOS found in human blood for different levels of exposition. The analysis of the factors contributing to the complex binding energy permitted to outline a set of guidelines for the rational design of alternative fluorinated surfactants with a lower bioaccumulation potential.		●		●						-		B	B
255	ADME	Tarazona, J V; Rodríguez, C; Alonso, E; Sáez, M; Gonzá lez, F; San Andrés, M D; Jim énez, B; San Andrés, M I	Toxicokinetics of perfluorooctane sulfonate in rabbits under environmentally realistic exposure conditions and comparative assessment between mammals and birds	2016	Toxicol Lett. 2016 Jan 22;241:200-6. doi: 10.1016/j.toxlet.2015.11.002. Epub 2015 Nov 10.	This article describes the toxicokinetics of perfluorooctane sulfonate (PFOS) in rabbits under low repeated dosing, equivalent to 0.085µg/kg per day, and the observed differences between rabbits and chickens. The best fitting for both species was provided by a simple pseudo monocompartmental first-order kinetics model, regulated by two rates, and accounting for real elimination as well as binding of PFOS to non-exchangeable structures. Elimination was more rapid in rabbits, with a pseudo first-order dissipation half-life of 88 days compared to the 230 days observed for chickens. By contrast, the calculated assimilation efficiency for rabbits was almost 1, very close to full absorption, significantly higher than the 0.66 with confidence intervals of 0.64 and 0.68 observed for chickens. The results confirm a very different kinetics than that observed in single-dose experiments confirming clear dose-related differences in apparent elimination rates in rabbits, as previously described for humans and other mammals; suggesting the role of a capacity-limited saturable process resulting in different kinetic behaviours for PFOS in high dose versus environmentally relevant low dose exposure conditions. The model calculations confirmed that the measured maximum concentrations were still far from the steady state situation, and that the different kinetics between birds and mammals should may play a significant role in the biomagnifications assessment and potential exposure for humans and predators. For the same dose regime, the steady state concentration was estimated at about 36µg PFOS/L serum for rabbits, slightly above one-half of the 65µg PFOS/L serum estimated for chickens. The toxicokinetic parameters presented here can be used for higher-tier bioaccumulation estimations of PFOS in rabbits and chickens as starting point for human health exposure assessments and as surrogate values for modeling PFOS kinetics in wild mammals and bird in exposure assessment of predatory species.				●						-		B	C
256	ADME	Tardiff, Robert G; Carson, M Leigh; Sweeney, Lisa M; Kirman, Christopher R; Tan, Yu-Mei; Andersen, Melvin; Bevan, Christopher; Gargas, Michael L	Derivation of a drinking water equivalent level (DWEL) related to the maximum contaminant level goal for perfluorooctanoic acid (PFOA), a persistent water soluble compound	2009	Food Chem Toxicol. 2009 Oct;47(10):2557-89. doi: 10.1016/j.fct.2009.07.016. Epub 2009 Jul 22.	Water soluble compounds persistent in humans and the environment pose a challenge for estimating safe levels in tap water. A viable approach to estimate a drinking water equivalent level (DWEL) for perfluorooctanoic acid (PFOA) was applied to its extensive relevant information from human and laboratory animal studies. PFOA has been identified at 3.5 microg/L (mean) in tap water in proximity to a manufacturing facility; however, in most supplies, the levels were below 7.5 ng/L (usual limit of detection). PFOA has an average half-life in humans of 3.5years. From animal studies, PFOA is considered a possible hepatotoxicant and developmental toxicant for humans. Based on two chronic studies, PFOA was judged to be a possible human carcinogen, whose mode-of-action was likely to be related to receptor activation but not genotoxicity. The Benchmark Dose-Uncertainty Factor approach was selected for dose-response for noncancer and cancer. Based on internal dose of PFOA, the DWEL protective against cancer is 7.7 microgPFOA/L tap water, and the noncancer DWELs range from 0.88 to 2.4 microg/L. These DWELs can be considered a reliable, albeit conservative, basis to set a Maximum Concentration Level Goal under the US Safe Drinking Water Act.				●						-		B	B
257	ADME	Vanden Heuvel, J P; Davis, J W 2nd; Sommers, R; Peterson, R E	Renal excretion of perfluorooctanoic acid in male rats: Inhibitory effect of testosterone	1992	J Biochem Toxicol. 1992 Spring;7(1):31-6. doi: 10.1002/jbt.2570070107.	There is a marked sex difference in the whole-body elimination of perfluorooctanoic acid (PFOA) in rats, with females excreting the perfluorinated acid much more rapidly (half life [t1/2] less than 1 day) than males (t1/2 = 15 days). Our objective was to determine if androgens or estrogens are involved in causing this sex difference in PFOA elimination. Castration of males greatly increased the elimination of [1-14C]PFOA (9.4 mumol/kg, i.p.) in urine, demonstrating that a factor produced by the testis was responsible for the slow elimination of PFOA in male rats. Castration plus 17 beta-estradiol had no further effect on PFOA elimination whereas castration plus testosterone replacement at the physiologic level reduced PFOA elimination to the same level as rats with intact testes. Thus, in male rats, testosterone exerts an inhibitory effect on renal excretion of PFOA. In female rats, neither ovariectomy nor ovariectomy plus testosterone affected the PFOA urinary elimination, demonstrating that the inhibitory effect of testosterone on PFOA renal excretion is a male-specific response. Probenecid decreased the high rate of PFOA renal excretion in castrated males but had no effect on male rats with intact testes. We conclude that testosterone is a key determinant of the sex difference in PFOA elimination in rats.				●						-		B	B
258	ADME	Vanden Heuvel, J P; Kuslikis, B I; Van Rafelghem, M J; Peterson, R E	Disposition of perfluorodecanoic acid in male and female rats	1991	Toxicol Appl Pharmacol. 1991 Mar 1;107(3):450-9. doi: 10.1016/0041-008x(91)90308-2.	The elimination, tissue distribution, and metabolism of [1-14C]PFDA were examined in male and female rats for 28 days after a single ip dose (9.4 mumol/kg, 5 mg/kg). A sex difference in the fecal elimination of perfluorodecanoic acid (PFDA) was observed with 51 and 24% of the administered 14C being recovered in the feces of male and female rats, respectively, by 28 days post-treatment. The cumulative excretion of PFDA-derived 14C in the urine in 28 days was less than 5% of the administered dose in both sexes. The sex-related difference in the rate of fecal elimination resulted in the observed difference in whole body elimination t1/2 of PFDA in males (t1/2 = 23 days) and females (t1/2 = 45 days). The liver contained the highest concentration of PFDA-derived 14C in both males and females, followed by the plasma and kidneys. The heart, fat pads, testes, and gastrocnemius muscle of males, and the ovaries of females contained much lower concentrations of PFDA. The reason for the high percentage of the ip dose of [1-14C]PFDA in the liver (53% males and 41% females, 2 hr post-treatment) was further examined using an in situ nonrecirculating liver perfusion technique. It was shown that approximately 25% of the [14C]PFDA in the perfusate was extracted by the liver in a single pass. The basis for the sex difference in fecal elimination of PFDA does not appear to be due to a sex difference in biliary excretion. In a 6-hr period, male and female rats with kidneys ligated eliminated essentially the same percentage dose of [14C]PFDA into bile. We had hypothesized that the persistence of PFDA in rats was due to formation of a PFDA-containing lipid (i.e., a [14C]PFDA-containing mono-, di-, or triacylglycerol, cholesteryl ester, methyl ester, or phospholipid). However, no evidence that PFDA is conjugated to form persistent hybrid lipids was obtained, nor were polar metabolites of PFDA detected in urine or bile. In addition, daily urinary excretion of fluoride in male and female rats before and after PFDA treatment was similar, suggesting that the parent compound is not defluorinated. Thus, the disposition of PFDA in male and female rats is characterized by an apparent lack of biotransformation.				●						-		C	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報収集対象抽出	文献ランク①	文献ランク②
259	ADME	Vanden Heuvel, J P; Kuslikis, B I; Van Rafelghem, M J; Peterson, R E	Tissue distribution, metabolism, and elimination of perfluorooctanoic acid in male and female rats	1991	J Biochem Toxicol. 1991 Summer;6(2):83-92. doi: 10.1002/jbt.2570060202.	The elimination, tissue distribution, and metabolism of [1-14C]perfluorooctanoic acid (PFOA) was examined in male and female rats for 28 days after a single ip dose (9.4 mumol/kg, 4 mg/kg). A sex difference in urinary elimination of PFOA-derived 14C was observed. Female rats eliminated PFOA-derived radioactivity rapidly in the urine with 91% of the dose being excreted in the first 24 hr. In the same period, male rats eliminated only 6% of the administered 14C in the urine. The sex-related difference in urinary elimination resulted in the observed difference in the whole-body elimination half-life (t1/2) of PFOA in males (t1/2 = 15 days) and females (t1/2 less than 1 day). Analysis of PFOA-derived 14C in tissues showed that the liver and plasma of male rats and the liver, plasma, and kidney of female rats were the primary tissues of distribution. The relatively high concentration of PFOA in the male liver was further examined using an in situ nonrecirculating liver perfusion technique. It was shown that 11% of the PFOA infused was extracted by the liver in a single pass. The ability of the liver to eliminate PFOA into bile was examined in rats whose renal pedicles were ligated to alleviate sex differences in the urinary excretion of PFOA. In a 6-hr period following IP administration of PFOA, there was no apparent difference in biliary excretion, where both males and females eliminated less than 1% of the PFOA dose via this route. We hypothesized that the sex difference in the persistence of PFOA was due to a more rapid formation of a PFOA-containing lipid (i.e., a PFOA-containing mono-, di-, or triacylglycerol, cholesteryl ester, methyl ester, or phospholipid) in the male rat. Also, the increased urinary elimination of PFOA in females may have been due to increased metabolism to a PFOA-glucuronide or sulfate ester. However, no evidence that PFOA is conjugated to form a persistent hybrid lipid was obtained, nor were polar metabolites of PFOA in urine or bile detected. In addition, daily urinary excretion of fluoride in male and female rats before or after PFOA treatment were similar, suggesting that the parent compound is not defluorinated. Thus, the more rapid elimination of PFOA from female rats is not due to formation of a PFOA metabolite.				●		●				-		B	B
260	ADME	Verner, Marc-André; Longnecker, Matthew P	Comment on "Enhanced elimination of perfluorooctanesulfonic acid by menstruating women: Evidence from population-based pharmacokinetic modeling	2015	Environ Sci Technol. 2015 May 5;49(9):5836-7. doi: 10.1021/acs.est.5b00187. Epub 2015 Apr 14.	No abstract provided.				●						コメント		D	D
261	ADME	Verner, Marc-André; Ngueta, Gérard; Jensen, Elizabeth T; Fromme, Hermann; Völkel, Wolfgang; Nygaard, Unni Cecilie; Granum, Berit; Longnecker, Matthew P	Correction to a simple pharmacokinetic model of prenatal and postnatal exposure to perfluoroalkyl substances (PFASs)	2016	Environ Sci Technol. 2016 May 17;50(10):5420-1. doi: 10.1021/acs.est.6b01755. Epub 2016 May 4.	No abstract provided.				●						修正論文		D	D
262	ADME	Wilhelm, Michael; Kraft, Martin; Rauchfuss, Knut; Hö lzer, Jürgen	Assessment and management of the first German case of a contamination with perfluorinated compounds (PFC) in the Region Sauerland, North Rhine-Westphalia	2008	J Toxicol Environ Health A. 2008;71(11-12):725-33. doi: 10.1080/15287390801985216.	In May 2006 the first serious German perfluorinated compounds (PFC) case of contamination became evident. Industrial waste with high concentrations of PFC was manufactured into a soil improver by a recycling company and spread by farmers on agricultural land of the rural area Sauerland, and led to substantial environmental pollution. In parts of the affected area, perfluorooctanoic acid (PFOA) concentrations in drinking water were > 0.5 microg/L. The German Drinking Water Commission assessed PFC in drinking water and set a health-based guidance value for safe lifelong exposure of all population groups at 0.3 microg/L (sum of perfluorooctane sulfonate [PFOS] and PFOA). The Ministry of Environment together with regional institutions initiated monitoring measurements and actions to minimize further contamination. A human biomonitoring study with mother-child pairs and men revealed that increased PFOA exposure via drinking water led to about four- to eightfold higher PFOA levels in plasma compared to nonexposed groups. Analysis of PFC in breast milk showed comparatively low levels, which seemed not to pose a risk for lactating infants. Due to high levels of PFOS in fish from contaminated lakes and rivers, recommendations for anglers to reduce fish consumption were initiated. Remediation of the affected area is ongoing and PFC levels in various matrices are still above background levels.				●		●				-		-	B
263	ADME	Yamada, Akihiro; Maeda, Kazuya; Kamiyama, Emi; Sugiyama, Daisuke; Kondo, Tsunenori; Shiroyanagi, Yoshiyuki; Nakazawa, Hayakazu; Okano, Teruo; Adachi, Masashi; Schuetz, John D; Adachi, Yasuhisa; Hu, Zhuohan; Kusuhara, Hiroyuki; Sugiyama, Yuichi	Multiple human isoforms of drug transporters contribute to the hepatic and renal transport of olmesartan, a selective antagonist of the angiotensin II AT1-receptor	2007	Drug Metab Dispos. 2007 Dec;35(12):2166-76. doi: 10.1124/dmd.107.017459. Epub 2007 Sep 6.	Olmesartan, a novel angiotensin II AT1-receptor antagonist, is excreted into both bile and urine, with minimal metabolism. Because olmesartan is a hydrophilic anionic compound, some transporters could be involved in its hepatic and renal clearance. In this study, we characterized the role of human drug transporters in the pharmacokinetics of olmesartan and determined the contribution of each transporter to the overall clearance of olmesartan. Olmesartan was significantly taken up into human embryonic kidney 293 cells expressing organic anion-transporting polypeptide (OATP) 1B1, OATP1B3, organic anion transporter (OAT) 1, and OAT3. We also observed its saturable uptake into human hepatocytes and kidney slices. Estimated from the relative activity factor method and application of specific inhibitors, the relative contributions of OATP1B1 and OATP1B3 to the uptake of olmesartan in human hepatocytes were almost the same, whereas OAT3 was predominantly involved in its uptake in kidney slices. The vectorial transport of olmesartan was observed in OATP1B1/multidrug resistance-associated protein (MRP) 2 double transfectants, but not in OATP1B1/multidrug resistance (MDR) 1 and OATP1B1/breast cancer resistance protein (BCRP) transfectants. ATP-dependent transport into membrane vesicles expressing human MRP2 and MRP4 was clearly observed, with K(m) values of 14.9 and 26.2 microM, respectively, whereas the urinary excretion of olmesartan in Mrp4-knockout mice was not different from that of control mice. We also investigated the transcellular transport of olmesartan medoxomil, a prodrug of olmesartan. Vectorial basal-to-apical transport was observed in OATP1B1/MRP2, OATP1B1/MDR1 double, and OATP1B1/BCRP double transfectants, suggesting the possible involvement of MRP2, MDR1, and BCRP in the limit of intestinal absorption of olmesartan medoxomil. From these results, we suggest that multiple transporters make a significant contribution to the pharmacokinetics of olmesartan and its prodrug.				●						-		C	C
264	ADME	Ylinen, M; Auriola, S	Tissue distribution and elimination of perfluorodecanoic acid in the rat after single intraperitoneal administration	1990	Pharmacol Toxicol. 1990 Jan;66(1):45-8. doi: 10.1111/j.1600-0773.1990.tb00700.x.	Tissue distribution, metabolism, and excretion of perfluorodecanoic acid (PFDA) after a single intraperitoneal dose (20 mg/kg) were studied in female and male Wistar rats. PFDA accumulated in the serum and tissues of the rats. In the serum, more than 99% of PFDA was bound by the serum proteins. In the liver, anionic and esterified PFDA were detected. Metabolic oxidation of PFDA was not observed. PFDA was not excreted in urine either by females or males during 14 days after the administration. At the same time, about 0.5% of the administered PFDA dose was excreted daily in the faeces by both sexes. In spite of the analogical structure with perfluorooctanoic acid (PFOA), which is rapidly eliminated in urine by the female rats, PFDA accumulated similarly in females and males. The reduced elimination of PFDA partially explains its greater toxicity to rats in comparison with PFOA.				●						-		C	C
265	ADME	Anzai, N; Kanai, Y; Endou, H.	Organic anion transporter family: current knowledge	2006	J Pharmacol Sci. 2006;100(5):411-26. doi: 10.1254/jphs.crj06006x.	Organic anion transporters (OATs) play an essential role in the elimination of numerous endogenous and exogenous organic anions from the body. The renal OATs contribute to the excretion of many drugs and their metabolites that are important in clinical medicine. Several families of multispecific organic anion and cation transporters, including OAT family transporters, have recently been identified by molecular cloning. The OAT family consists of six isoforms (OAT1 - 4, URAT1, and rodent Oat5) and they are all expressed in the kidney, while some are also expressed in the liver, brain, and placenta. The OAT family represents mainly the renal secretory and reabsorptive pathway for organic anions and is also involved in the distribution of organic anions in the body, drug-drug interactions, and toxicity of anionic substances such as nephrotoxic drugs and uremic toxins. In this review, current knowledge of and recent progress in the understanding of several aspects of OAT family members are discussed.		●								-		C	C
266	ADME	Chen, Fangfang; Yin, Shanshan; Kelly, Barry C; Liu, Weiping	Chlorinated polyfluoroalkyl ether sulfonic acids in matched maternal, cord, and placenta samples: A study of transplacental transfer	2017	Environ Sci Technol. 2017 Jun 6;51(11):6387-6394. doi: 10.1021/acs.est.6b06049. Epub 2017 May 12.	Currently, information regarding concentrations of chlorinated polyfluoroalkyl ether sulfonic acids (Cl-PFESAs) in human placenta does not exist. The main objective of this study was to assess the occurrence and distribution of two Cl-PFESAs, 6:2 Cl-PFESA and 8:2 Cl-PFESA, in maternal serum, umbilical cord serum, and placenta to better assess the transport pathways related to human prenatal exposure. The widely studied perfluorooctanesulfonate (PFOS) was studied for comparison. This study was a hospital-based survey involving quantitative determination of Cl-PFESA and PFOS concentrations in maternal serum (n = 32), cord serum (n = 32), and placenta (n = 32) samples from women in Wuhan, China. The results indicate that Cl-PFESAs can efficiently be transported across placenta, with median exposure levels of 0.60 and 0.01 ng/mL for 6:2 Cl-PFESA and 8:2 Cl-PFESA in the cord sera, respectively. Concentrations of the target compounds in maternal sera, cord sera, and placentas decreased in the following order: PFOS > 6:2 Cl-PFESA > 8:2 Cl-PFESA. Similar patterns were observed in maternal sera, cord sera, and placentas for Cl-PFESAs, with concentrations decreasing in the following order: maternal sera > cord sera > placentas. Significant correlations were observed among 6:2 Cl-PFESA, 8:2 Cl-PFESA, and PFOS concentrations in the maternal serum, cord serum, and placenta samples (r > 0.7; p < 0.001). The median value of R(CM) (ratio of cord serum to maternal serum concentration) of 6:2 Cl-PFESA was 0.403, indicating a relatively high (圩ｼ40%) placental transfer efficiency. 8:2 Cl-PFESA was transported across placenta to a greater extent than 6:2 Cl-PFESA was, likely because of its higher hydrophobicity and lower plasma protein binding affinity. To the best of our knowledge, this is the first study to report the occurrence and distribution of 6:2 Cl-PFESA and 8:2 Cl-PFESA in human placenta. The findings improve our understanding of the mechanisms of transplacental transfer and neonatal exposure to these important PFOS alternatives.		●								-		C	B
267	ADME	Hanhijarvi, H; Ophaug, RH; Singer, L.	THE SEX-RELATED DIFFERENCE IN PERFLUOROOCTANOATE EXCRETION IN THE RAT.	1982	Proc Soc Exp Biol Med. 1982 Oct;171(1):50-5. doi: 10.3181/00379727-171-41476.	No abstract available		●								140と重複→削除予定		D	D

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報抽出対象	文献ランク①	文献ランク②
268	ADME	Li, Y; Yu, N; Du, L; Shi, W; Yu, H; Song, M; Wei, S.	Transplacental Transfer of Per- and Polyfluoroalkyl Substances Identified in Paired Maternal and Cord Sera Using Suspect and Nontarget Screening	2020	Environ Sci Technol. 2020 Mar 17;54(6):3407-3416. doi: 10.1021/acs.est.9b06505. Epub 2020 Feb 25.	Novel per- and polyfluoroalkyl substances (PFASs) in various environmental media have attracted increasing attention; however, the information regarding PFASs exposure in pregnant women and fetuses is insufficient. In this study, we built and applied suspect and nontarget screening strategies based on the mass difference of the CF2, CF2O, and CH2CF2 units to select potential novel PFASs from 117 paired maternal and cord sera. In total, 10 legacy PFASs and 19 novel PFASs from 10 classes were identified to be above confidence levels 3, among which 14 were not previously reported in human serum. Novel PFASs accounted for a considerable percentage of total PFASs in pregnant women and can be transferred to fetuses at non-negligible concentrations (i.e., 27.9% and 30.3% of total PFAS intensities in maternal and cord sera, respectively). The transplacental transfer efficiency (TTE) of PFASs showed a U-shape trend in the series of perfluoroalkyl carboxylic acids, perfluoroalkyl sulfonic acids, and unsaturated perfluorinated alcohols. The TTE of novel PFASs is suggested to be structure-dependent, based on a flexible docking experiment. This study provides comprehensive TTE information on legacy and novel PFASs for the first time, and additional toxicity studies are needed to evaluate the risk of novel PFASs further.		●								-		B	B
269	ADME	Mylchreest, E.	PFOA: Lactational and Placental Transport Pharmacokinetic Study in Rats. (DuPont-13309)	2003	Newark, DE: Haskell Laboratory for Health and Environmental Sciences.	No abstract available	●									企業データ		D	D
270	ADME	Wu, LL; Gao, HW; Gao, NY; Chen, FF; Chen, L.	Interaction of perfluorooctanoic acid with human serum albumin	2009	BMC Struct Biol. 2009 May 14;9:31. doi: 10.1186/1472-6807-9-31.	Background: Recently, perfluorooctanoic acid (PFOA) has become a significant issue in many aspects of environmental ecology, toxicology, pathology and life sciences because it may have serious effects on the endocrine, immune and nervous systems and can lead to embryonic deformities and other diseases. Human serum albumin (HSA) is the major protein component of blood plasma and is called a multifunctional plasma carrier protein because of its ability to bind an unusually broad spectrum of ligands. Results: The interaction of PFOA with HSA was investigated in the normal physiological condition by equilibrium dialysis, fluorospectrometry, isothermal titration calorimetry (ITC) and circular dichroism (CD). The non-covalent interaction is resulted from hydrogen bond, van der Waals force and hydrophobic stack. PFOA binding to HSA accorded with two-step binding model with the saturation binding numbers of PFOA, only 1 in the hydrophobic intracavity of HSA and 12 on the exposed outer surface. The interaction of PFOA with HSA is spontaneous and results in change of HSA conformation. The possible binding sites were speculated. Conclusion: The present work suggested a characterization method for the intermolecular weak interaction. It is potentially useful for elucidating the toxigenicity of perfluorochemicals when combined with biomolecular function effect, transmembrane transport, toxicological testing and the other experiments.		●								-		B	B
271	ADME	Zhao, L. X.; Zhang, Y. F.; Zhu, L. Y.; Ma, X. X.; Wang, Y.; Sun, H. W.; Luo, Y.	Isomer-Specific Transplacental Efficiencies of Perfluoroalkyl Substances in Human Whole Blood	2017	Environ Sci Technol Lett. 4: 391-398. doi: 10.1021/acs.estlett.7b00334	Data on isomer-specific transplacental transfer of perfluoroalkyl substances (PFASs) are very scarce. This study investigates transplacental transfer of 23 PFASs, including isomers of perfluorooctanoate (PFOA) and perfluorooctanesulfonate (PFOS), by analyzing 63 paired maternal and cord whole blood samples collected in Hubei, China. Significant correlations (r = 0.311-0.888; p <= 0.013) were observed between the concentrations in maternal and cord blood for most PFASs, indicating that PFASs could be efficiently transported from mother to fetus. For perfluorocarboxylates, a U-shaped trend of transplacental transfer efficiencies (TTEs) with increasing carbon chain lengths was confirmed. For PFOA and PFOS branched isomers, TTEs generally increased as the branching point moved closer to the carboxyl or sulfonate moiety, and branched isomers transferred more efficiently than their linear isomers did. This is the first report of the TTEs of PFAS isomers based on human whole blood samples and the first calculation of the TTEs of perfluorooctane sulfonamide. For almost all PFASs, the TTEs we reported are lower than those from previous studies based on serum or plasma. Whole blood is recommended for risk assessment of PFAS placental transfer considering that PFASs exhibit different partitioning behaviors between blood matrices. More accurate parameters for the health risks of PFASs during prenatal exposure are provided here.		●								-		B	B
272	ADME	Haber, L.T., Dourson, M.L. and Mohapatra A.	Development of chemical-specific adjustment factors for long-lived chemicals: PFOS as a model chemicals: PFOS as a model chemical.	2013	Poster presented at Society for Risk Analysis Annual Meeting, Baltimore, MD, December 8–11.	No abstract available					●	●				ポスター		D	D
273	ADME	Johnson, J.D. and Ober, R.E.	Absorption of FC-143-14C in rats after a single oral dose	1999	In: Exploratory 28-day oral toxicity study with telomer alcohol, telomer acrylate, PFHS, and PFOS (POS control) by daily gavage in the rat, w/CVR LTR DTD, 051500 (Sanitized) 3M. Submitted to the U.S. Environmental Protection Agency under TSCA Section FYI. OTS05001378S. [As cited in ATSDR (2009)].	No abstract available					●					企業データ		D	D
274	ADME	Kadar, Hanane; Veyrand, Bruno; Barbarossa, Andrea; Pagliuca, Giampiero; Legrand, Arnaud; Bosher, Cécile; Boquien, Clair-Yves; Durand, Sophie; Monteau, Fabrice; Antignac, Jean-Philippe; Le Bizec, Bruno	Development of an analytical strategy based on liquid chromatography-high resolution mass spectrometry for measuring perfluorinated compounds in human breast milk: application to the generation of preliminary data regarding perinatal exposure in France	2011	Chemosphere. 2011 Oct;85(3):473-80. doi: 10.1016/j.chemosphere.2011.07.077. Epub 2011 Aug 30.	Perfluorinated compounds (PFCs) are man-made chemicals for which endocrine disrupting properties and related possible side effects on human health have been reported, particularly in the case of an exposure during the early stages of development, (notably the perinatal period). Existing analytical methods dedicated to PFCs monitoring in food and/or human fluids are currently based on liquid chromatography coupled to tandem mass spectrometry, and were recently demonstrated to present some limitations in terms of sensitivity and/or specificity. An alternative strategy dedicated to the analysis of fourteen PFCs in human breast milk was proposed, based on an effective sample preparation followed by a liquid chromatography coupled to high resolution mass spectrometry measurement (LC-HRMS). This methodology confirmed the high interest for HRMS after negative ionization for such halogenated substances, and finally permitted to reach detection limits around the pg mL(-1) range with an outstanding signal specificity compared to LC-MS/MS. The proposed method was applied to a first set of 30 breast milk samples from French women. The main PFCs detected in all these samples were PFOS and PFOA with respective median values of 74 (range from 24 to 171) and 57 (range from 18 to 102) pg mL(-1), respectively. These exposure data appeared in the same range as other reported values for European countries.					●	●				-		B	B
275	ADME	Lau, C.; Anitole, K.; Hodes, C.; Lai, D.; Pfahles-Hutchens, A.; Seed, J.	Perfluoroalkyl acids: a review of monitoring and toxicological findings	2007	Toxicol Sci. 2007 Oct;99(2):366-94. doi: 10.1093/toxsci/kfm128. Epub 2007 May 22.	In recent years, human and wildlife monitoring studies have identified perfluoroalkyl acids (PFAA) worldwide. This has led to efforts to better understand the hazards that may be inherent in these compounds, as well as the global distribution of the PFAAs. Much attention has focused on understanding the toxicology of the two most widely known PFAAs, perfluorooctanoic acid, and perfluorooctane sulfate. More recently, research was extended to other PFAAs. There has been substantial progress in understanding additional aspects of the toxicology of these compounds, particularly related to the developmental toxicity, immunotoxicity, hepatotoxicity, and the potential modes of action. This review provides an overview of the recent advances in the toxicology and mode of action for PFAAs, and of the monitoring data now available for the environment, wildlife, and humans. Several avenues of research are proposed that would further our understanding of this class of compounds.					●	●	●			-		B	B
276	ADME	Roosens, Laurence; D'Hollander, Wendy; Bervoets, Lieven; Reynders, Hans; Van Campenhout, Karen; Cornelis, Christa; Van Den Heuvel, Rosette; Koppen, Gudrun; Covaci, Adrian	Brominated flame retardants and perfluorinated chemicals, two groups of persistent contaminants in Belgian human blood and milk	2010	Environ Pollut. 2010 Aug;158(8):2546-52. doi: 10.1016/j.envpol.2010.05.022. Epub 2010 Jun 22.	We assessed the exposure of the Flemish population to brominated flame retardants (BFRs) and perfluorinated compounds (PFCs) by analysis of pooled cord blood, adolescent and adult serum, and human milk. Levels of polybrominated diphenyl ethers (PBDEs) in blood (range 1.6-6.5 ng/g lipid weight, lw) and milk (range 2.0-6.4 ng/g lw) agreed with European data. Hexabromocyclododecane ranged between <2.1-5.7 ng/g lw in milk. Perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) dominated in blood and ranged between 1 and 171 ng/mL and <0.9-9.5 ng/mL, respectively. Total PFC levels in milk ranged between <0.5-29 ng/mL. A significant increase in PBDE concentrations was detected from newborns (median 2.1) to the adolescents and adults (medians 3.8 and 4.6 ng/g lw, respectively). An identical trend was observed for PFOS, but not for PFOA. We estimated that newborn exposure to BFRs and PFCs occurs predominantly post-natally, whereas placental transfer has a minor impact on the body burden.					●					-		B	B
277	ADME	Summit Toxicology	Interspecies extrapolation for perfluorooctyl sulfonate (PFOS) and perfluorooctanoic acid (PFOA)	2015	Summit Toxicology, L.L.P. Report submitted to Health Canada.	No abstract available					●	●				企業データ		D	D
278	ADME	ATSDR	Toxicological profile for perfluoroalkyls, draft for public comment	2009	Agency for Toxic Substances and Disease Registry Available at: www.atsdr.cdc.gov/toxprofiles/tp.asp?id=1117&tid=237	No abstract available						●				評価書		D	D
279	ADME	Johnson, J.D. and Ober, R.E.	Absorption of FC-143-14C in rats after a single oral dose	1999	In: Exploratory 28-day oral toxicity study with telomer alcohol, telomer acrylate, PFHS, and PFOS (POS control) by daily gavage in the rat, w/CVR LTR DTD, 051500 (Sanitized) 3M. Submitted to the U.S. Environmental Protection Agency under TSCA Section FYI. OTS05001378S. [cited in ATSDR (2009)].	No abstract available						●				企業データ		D	D
280	ADME	Xie, Wei; Ludewig, Gabriele; Wang, Kai; Lehmler, Hans-Joachim	Model and cell membrane partitioning of perfluorooctanesulfonate is independent of the lipid chain length	2010	Colloids Surf B Biointerfaces. 2010 Mar 1;76(1):128-36. doi: 10.1016/j.colsurfb.2009.10.025. Epub 2009 Oct 27.	Perfluorooctanesulfonic acid (PFOS) is a persistent environmental pollutant that may cause adverse health effects in humans and animals by interacting with and disturbing of the normal properties of biological lipid assemblies. To gain further insights into these interactions, we investigated the effect of PFOS potassium salt on dimyristoyl- (DMPC), dipalmitoyl- (DPPC) and distearoylphosphatidylcholine (DSPC) model membranes using fluorescence anisotropy measurements and differential scanning calorimetry (DSC) and on the cell membrane of HL-60 human leukemia cells and freshly isolated rat alveolar macrophages using fluorescence anisotropy measurements. PFOS produced a concentration-dependent decrease of the main phase transition temperature (T(m)) and an increased peak width (DeltaT(w)) in both the fluorescence anisotropy and the DSC experiments, with a rank order DMPC>DPPC>DSPC. PFOS caused a fluidization of the gel phase of all phosphatidylcholines investigated, but had the opposite effect on the liquid-crystalline phase. The apparent partition coefficients of PFOS between the phosphatidylcholine bilayer and the bulk aqueous phase were largely independent of the phosphatidylcholine chain length and ranged from 4.4x10(4) to 8.8x10(4). PFOS also significantly increased the fluidity of membranes of cells. These findings suggest that PFOS readily partitions into lipid assemblies, independent of their composition, and may cause adverse biological effects by altering their fluidity in a manner that depends on the membrane cooperativity and state (e.g., gel versus liquid-crystalline phase) of the lipid assembly.							●			-		B	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献ラン①	文献ラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
281	ADME	Morita, Yasuko; Homma, Yasuhiko; Igarashi, Mihoko; Miyano, Ryuusuke; Yamaguchi, Hiroshi; Matsuda, Momoo; Tanigaki, Toshimori; Shiina, Yutaka; Homma, Koichiro	Decrease in glomerular filtration rate by plasma low density lipoprotein cholesterol in subjects with normal kidney function assessed by urinalysis and plasma creatinine Atherosclerosis 210(2): 602-606	2010	Atherosclerosis. 2010 Jun;210(2):602-6. doi: 10.1016/j.atherosclerosis.2009.12.025. Epub 2009 Dec 29.	OBJECTIVE: It has not been well defined whether plasma low-density lipoprotein cholesterol (LDL-C) progresses arteriolosclerosis (arteriosclerosis of small arteries) or not. Estimated glomerular filtration rate (e-GFR) is an indicator of the function of renal arterioles and capillaries of glomeruli. The relationship between e-GFR and plasma LDL-C was studied to estimate the effect of plasma LDL-C on the function of renal arterioles and capillaries of glomeruli to speculate the effect of plasma LDL-C on arteriolosclerosis. METHODS AND RESULTS: Major coronary risk factors; blood pressure, plasma lipids, and fasting plasma glucose were compared among 4 groups of examinees of a health evaluation and promotion center separated by e-GFR, namely, Control group, Group 1, 2, 3 from highest e-GFR to lowest e-GFR. Numbers of total male and female subjects were 4602 and 2920, respectively. Plasma LDL-C levels were significantly high in Group 2 and 3 in all male subjects and high in Group 1, 2, and 3 in male subjects with age of fifties, compared with Control group. Plasma LDL-C levels were significantly high in Group 1, 2, and 3 in all female subjects and high in Group 2 and 3 in female subjects with age of fifties, compared with Control group. Plasma levels of LDL-C were not significantly different at each years of age in subjects with age of fifties in both sex. BMI and waist circumference were higher in male subjects with low e-GFR but not in female subjects. Blood pressure and fasting plasma glucose were not high in subjects in Group 1, 2, and 3, compared with Control group in all subjects and subjects with age of fifties in both sex. CONCLUSIONS: We concluded that the high plasma level of LDL-C was the major risk factor among coronary risk factors to reduce GFR probably due to impairing the function of renal arterioles and capillaries of glomeruli in subjects with normal kidney function assessed by urinalysis and plasma creatinine.						●			-		C	C
282	ADME	Sheng, Nan; Li, Juan; Liu, Hui; Zhang, Aiqian; Dai, Jiayin	Interactions of Perfluoroalkyl acids with human liver fatty acid-binding protein	2016	Arch Toxicol. 2016 Jan;90(1):217-27. doi: 10.1007/s00204-014-1391-7. Epub 2014 Nov 5.	Perfluoroalkyl acids (PFAAs) are highly persistent and bioaccumulative, resulting in their broad distribution in humans and the environment. The liver is an important target for PFAAs, but the mechanisms behind PFAAs interaction with hepatocyte proteins remain poorly understood. We characterized the binding of PFAAs to human liver fatty acid-binding protein (hL-FABP) and identified critical structural features in their interaction. The binding interaction of PFAAs with hL-FABP was determined by fluorescence displacement and isothermal titration calorimetry (ITC) assay. Molecular simulation was conducted to define interactions at the binding sites. ITC measurement revealed that PFOA/PFNA displayed a moderate affinity for hL-FABP at a 1:1 molar ratio, a weak binding affinity for PFHxS and no binding for PFHxA. Moreover, the interaction was mainly mediated by electrostatic attraction and hydrogen bonding. Substitution of Asn111 with Asp caused loss of binding affinity to PFAA, indicating its crucial role for the initial PFAA binding to the outer binding site. Substitution of Arg122 with Gly caused only one molecule of PFAA to bind to hL-FABP. Molecular simulation showed that substitution of Arg122 increased the volume of the outer binding pocket, making it impossible to form intensive hydrophobic stacking and hydrogen bonds with PFOA, and highlighting its crucial role in the binding process. The binding affinity of PFAAs increased significantly with their carbon number. Arg122 and Asn111 played a pivotal role in these interactions. Our findings may help understand the distribution pattern, bioaccumulation, elimination, and toxicity of PFAAs in humans.						●			-		B	B
283	ADME	Campbell, Jerry; Clewell, Harvey; Cox, Tony; Dourson, Michael; Ethridge, Shannon; Forsberg, Norman; Gadagbui, Bernard; Hamade, Ali; Naidu, Ravi; Pechacek, Nathan; Peixe, Tiago Severo; Prueitt, Robyn; Rachamalla, Mahesh; Rhomberg, Lorenz; Smith, James; Verma, Nitin	The Conundrum of the PFOA human half-life, an international collaboration	2022	Regul Toxicol Pharmacol. 2022 Jul;132:105185. doi: 10.1016/j.yrtph.2022.105185. Epub 2022 May 7.	The Steering Committee of the Alliance for Risk Assessment (ARA) opened a call for scientists interested in resolving what appeared to be a conundrum in estimating of the half-life of perfluorooctanoate (PFOA) in humans. An Advisory Committee was formed from nominations received and a subsequent invitation led to the development of three small independent working groups to review appropriate information and attempt a resolution. Initial findings were shared among these groups and a conclusion developed from the ensuing discussions. Many human observational studies have estimated the PFOA half-life. Most of these studies note the likely occurrence of unmonitored PFOA exposures, which could inflate values of the estimated PFOA half-life. Also, few of these studies estimated the half-life of PFOA isomers, the branched chains of which likely have shorter half-lives. This could deflate values of the estimated linear PFOA half-life. Fortunately, several studies informed both of these potential problems. The majority opinion of this international collaboration is that the studies striking the best balance in addressing some of these uncertainties indicate the likely central tendency of the human PFOA half-life is less than 2 years. The single best value appears to be the geometric mean (GM) of 1.3 years (Zhang et al., 2013, Table 3), based on a GM = 1.7 years in young females (n = 20) and GM = 1.2 years in males of all ages and older females (n = 66). However, a combined median value from Zhang et al. (2013) of 1.8 years also adds value to this range of central tendency. While the Collaboration found this study to be the least encumbered with unmonitored PFOA exposures and branched isomers, more studies of similar design would be valuable. Also valuable would be clarification around background exposures in other existing studies in case adjustments to half-life estimates are attempted.								●	-		B	B
284	ADME	Campbell, Jerry; Clewell, Harvey; Cox, Tony; Dourson, Michael; Ethridge, Shannon; Forsberg, Norman; Gadagbui, Bernard; Hamade, Ali; Naidu, Ravi; Pechacek, Nathan; Peixe, Tiago Severo; Prueitt, Robyn; Rachamalla, Mahesh; Rhomberg, Lorenz; Smith, James; Verma, Nitin	Response to letter to editor "letter to the editors regarding "the Conundrum of the PFOA human half-life, an international collaboration	2022	Regul Toxicol Pharmacol. 2022 Oct;134:105246. doi: 10.1016/j.yrtph.2022.105246. Epub 2022 Aug 12.	No abstract available								●	-		B	D
285	ADME	Ducatman, Alan; Luster, Michael; Fletcher, Tony	Perfluoroalkyl substance excretion: Effects of organic anioninhibiting and resin-binding drugs in a community setting	2021	Environ Toxicol Pharmacol. 2021 Jul;85:103650. doi: 10.1016/j.etap.2021.103650. Epub 2021 Apr 2.	BACKGROUND: Longer serum half-lives of perfluoroalkyl substances (PFAS) in humans compared to other species has been attributed to differences in the activity of organic anion transporters (OAT). METHODS: Among 56,175 adult participants in the community-based C8 Health Project, 23 subjects were taking the uricosuric OAT-inhibitor probenecid, and 36 subjects were taking the bile acid sequestrant cholestyramine. In regression models of log transformed serum PFAS, medication effects were estimated in terms of mean ratios, adjusting for age, gender, BMI, estimated glomerular filtration rate (eGFR) and water-district of residence. RESULTS: Probenecid was associated with modest, but not statistically significant increases in serum PFAS concentrations. In contrast, cholestyramine significantly lowered serum PFAS concentrations, notably for perfluorooctane sulfonic acid (PFOS). CONCLUSIONS: The effectiveness of cholestyramine in a community setting supports the importance of gastrointestinal physiology for PFAS excretion kinetics, especially for PFOS. We did not find clear evidence that probenecid, an inhibitor of OAT, affects PFAS clearance.								●	-		A	B
286	ADME	Post, Gloria B; Birnbaum, Linda S; DeWitt, Jamie C; Goeden, Helen; Heiger-Bernays, Wendy J; Schlezinger, Jennifer J	Letter to the editors regarding "The conundrum of the PFOA human half-life, an international collaboration"	2022	Regul Toxicol Pharmacol. 2022 Oct;134:105240. doi: 10.1016/j.yrtph.2022.105240. Epub 2022 Aug 13.	No abstract available								●	-		B	D
287	TK	Bartell, S. M.; Calafat, A. M.; Lyu, C.; Kato, K.; Ryan, P. B.; Steenland, K.	Rate of Decline in Serum PFOA Concentrations after Granular Activated Carbon Filtration at Two Public Water Systems in Ohio and West Virginia	2010	Environ Health Perspect. 2010 Feb;118(2):222-8. doi: 10.1289/ehp.0901252.	Background: Drinking water in multiple water districts in the Mid-Ohio Valley has been contaminated with perfluorooctanoic acid (PFOA), which was released by a nearby DuPont chemical plant. Two highly contaminated water districts began granular activated carbon filtration in 2007.Objectives: To determine the rate of decline in serum PFOA, and its corresponding half-life, during the first year after filtration.Methods: Up to six blood samples were collected from each of 200 participants from May 2007 until August 2008 The primary source of drinking water varied over time for some participants; our analyses were grouped according to water source at baseline in MayJune 2007.Results: For Lubeck Public Service District customers, the average decrease in serum PFOA concentrations between MayJune 2007 and MayAugust 2008 was 32 ng/mL -0.26 for those primarily consuming public water at home (n = 130), and 16 ng/mL -0.28 for those primarily consuming bottled water at home (n = 17). For Little Hocking Water Association customers, the average decrease in serum PFOA concentrations between NovemberDecember 2007 and MayJune 2008 was 39 ng/mL -0.11 for consumers of public water (n = 39) and 28 ng/mL -0.2 for consumers of bottled water (n = 11). The covariate-adjusted average rate of decrease in serum PFOA concentration after water filtration was 0.26 per year (95% confidence interval, 25.28 per year).Conclusions: The observed data are consistent with first-order elimination and a median serum PFOA half-life of 2.3 years. Ongoing follow-up will lead to improved half-life estimation. Editor's SummaryRelease of perfluorooctanoic acid (PFOA) from a chemical plant in West Virginia contaminated drinking water in several water districts, but use of granular activated-carbon filtration in two water districts reduced PFOA concentrations to levels below the limit of detection. Bartell et al. (p. 222) measured serum PFOA concentrations in up to six blood samples collected over approximately 12 months from a stratified random sample of 200 eligible participants in the C8 Health Project cohort, including baseline samples collected before initiation of water filtration to remove PFOA. The authors report that the average covariate-adjusted average rate of decrease in serum PFOA concentration after water filtration was 0.26 per year [95% confidence interval (CI), 25.28 per year], consistent with a median serum PFOA half-life of 2.3 years (95% CI, 2.12.4 years). However, the authors also noted substantial variation in estimated half-lives among individuals, which may reflect ongoing exposures among some participants (e.g., through consumption of contaminated home-grown produce) and/or individual	●	●	●	●		●				-		A	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報抽出対象	文献ランク①	文献ランク②
288	TK	Benskin, J. P.; De Silva, A. O.; Martin, L. J.; Arsenault, G.; Mccrindle, R.; Riddell, N.; Mabury, S. A.; Martin, J. W.	Disposition of perfluorinated acid isomers in Sprague-Dawley rats; part 1: single dose	2009	Environ Toxicol Chem. 2009 Mar;28(3):542-54. doi: 10.1897/08-239.1. Epub 2008 Oct 21.	Perfluorinated acids (PFAs) and their precursors (PFA-precursors) exist in the environment as linear and multiple branched isomers. These isomers are hypothesized to have different biological properties, but no isomer-specific data are currently available. The present study is the first in a two-part project examining PFA isomer-specific uptake, tissue distribution, and elimination in a rodent model. Seven male Sprague-Dawley rats were administered a single gavage dose of approximately 500 microg/kg body weight perfluorooctane sulfonate (C(8)F(17)SO(3)(-), PFOS), perfluorooctanoic acid (C(7)F(15)CO(2)H, PFOA), and perfluorononanoic acid (C(8)F(17)CO(2)H, PFNA) and 30 microg/kg body weight perfluorohexane sulfonate (C(6)F(13)SO(3)(-), PFHxS). Over the subsequent 38 d, urine, feces, and tail-vein blood samples were collected intermittently, while larger blood volumes and tissues were collected on days 3 and 38 for isomer analysis by high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS). For all PFAs, branched isomers generally had lower blood depuration half-lives than the corresponding linear isomer. The most remarkable exception was for the PFOS isomer containing an alpha-perfluoromethyl branch (1m-PFOS), which was threefold more persistent than linear PFOS, possibly due to steric shielding of the hydrophilic sulfonate moiety. For perfluoromonomethyl-branched isomers of PFOS, a structure-property relationship was observed whereby branching toward the sulfonate end of the perfluoroalkyl chain resulted in increased half-lives. For PFHxS, PFOA, and PFOS, preferential elimination of branched isomers occurred primarily via urine, whereas for PFNA preferential elimination of the isopropyl isomer occurred via both urine and feces. Changes in the blood isomer profiles over time and their inverse correlation to isomer elimination patterns in urine, feces, or both provided unequivocal evidence of significant isomer-specific biological handling. Source assignment based on PFA isomer profiles in biota must therefore be conducted with caution, because isomer profiles are unlikely to be conserved in biological samples.	●	●	●	●	●					-		B	B
289	TK	Butenhoff, J. L.; Kennedy, G. L.; Hinderliter, P. M.; Lieder, P. H.; Jung, R.; Hansen, K. J.; Gorman, G. S.; Noker, P. E.; Thomford, P. J.	Pharmacokinetics of perfluorooctanoate in cynomolgus monkeys	2004	Toxicol Sci. 2004 Dec;82(2):394-406. doi: 10.1093/toxsci/kfh302. Epub 2004 Oct 6.	The pharmacokinetics of perfluorooctanoate (PFOA) in cynomolgus monkeys were studied in a six-month oral capsule dosing study of ammonium perfluorooctanoate (APFO) and in a single-dose iv study. In the oral study, samples of serum, urine, and feces were collected every two weeks from monkeys given daily doses of either 0, 3, 10, or 20 mg APFO/kg. Steady-state was reached within four weeks in serum, urine, and feces. Serum PFOA followed first-order elimination kinetics after the last dose, with a half-life of approximately 20 days. Urine was the primary elimination route. Mean serum PFOA concentrations at steady state in the 3, 10, and 20 mg/kg-day dose groups, respectively, were 81, 99, and 156 microg/ml in serum; 53, 166, and 181 microg/ml in urine; and, 7, 28, and 50 microg/g in feces. Mean liver concentrations reached 16, 14, and 50 microg/g in the 3, 10, and 20 mg/kg groups, respectively. In the iv study, three monkeys per sex were given a single dose of 10 mg/kg potassium PFOA. Samples were collected through 123 days. The terminal half-life of PFOA in serum was 13.6, 13.7, and 35.3 days in the three male monkeys and 26.8, 29.3, and 41.7 days in the three females. Volume of distribution at steady state was 181 +/- 12 and 198 +/- 69 ml/kg for males and females, respectively. Based on the result of both the oral and iv studies, the elimination half-life is approximately 14-42 days, and urine is the primary route of excretion.	●	●	●	●		●			●	-		A	B
290	TK	Chang, S. C.; Noker, P. E.; Gorman, G. S.; Gibson, S. J.; Hart, J. A.; Ehresman, D. J.; Butenhoff, J. L.	Comparative pharmacokinetics of perfluorooctanesulfonate (PFOS) in rats, mice, and monkeys	2012	Reprod Toxicol. 2012 Jul;33(4):428-440. doi: 10.1016/j.reprotox.2011.07.002. Epub 2011 Aug 11.	Perfluorooctanesulfonate (PFOS) has been found in biological samples in wildlife and humans. The geometric mean half-life of serum elimination of PFOS in humans has been estimated to be 4.8 years (95% CI, 4.0-5.8). A series of studies was undertaken to establish pharmacokinetic parameters for PFOS in rats, mice, and monkeys after single oral and/or IV administration of K(+)PFOS. Animals were followed for up to 23 weeks, and pharmacokinetic parameters were determined by WinNonlin® software. Rats and mice appeared to be more effective at eliminating PFOS than monkeys. The serum elimination half-lives in the rodent species were on the order of 44563 months; whereas, in monkeys, the serum elimination half lives approximated 4 months. Collectively, these studies provide valuable insight for human health risk assessment regarding the potential for accumulation of body burden in humans on repeated exposure to PFOS and PFOS-generating materials.	●	●	●	●	●				●	-		A	B
291	TK	Chou, W. C.; Lin, Z.	Bayesian evaluation of a physiologically based pharmacokinetic (PBPK) model for perfluorooctane sulfonate (PFOS) to characterize the interspecies uncertainty between mice, rats, monkeys, and humans: Development and performance verification	2019	Environ Int. 2019 Aug;129:408-422. doi: 10.1016/j.envint.2019.03.058. Epub 2019 May 29.	A challenge in the risk assessment of perfluorooctane sulfonate (PFOS) is the large interspecies differences in its toxicokinetics that results in substantial uncertainty in the dosimetry and toxicity extrapolation from animals to humans. To address this challenge, the objective of this study was to develop an open-source physiologically based pharmacokinetic (PBPK) model accounting for species-specific toxicokinetic parameters of PFOS. Considering available knowledge about the toxicokinetic properties of PFOS, a PBPK model for PFOS in mice, rats, monkeys, and humans after intravenous and oral administrations was created. Available species-specific toxicokinetic data were used for model calibration and optimization, and independent datasets were used for model evaluation. Bayesian statistical analysis using Markov chain Monte Carlo (MCMC) simulation was performed to optimize the model and to characterize the uncertainty and interspecies variability of chemical-specific parameters. The model predictions well correlated with the majority of datasets for all four species, and the model was validated with independent data in rats, monkeys, and humans. The model was applied to predict human equivalent doses (HEDs) based on reported points of departure in selected critical toxicity studies in rats and monkeys following U.S. EPA's guidelines. The lower bounds of the model-derived HEDs were overall lower than the HEDs estimated by U.S. EPA (e.g., 0.2 vs. 1.3 μg/kg/day based on the rat plasma data). This integrated and comparative analysis provides an important step towards improving interspecies extrapolation and quantitative risk assessment of PFOS, and this open-source model provides a foundation for developing models for other perfluoroalkyl substances.	●	●	●							-		B	B
292	TK	Dzierlenga, A. L.; Robinson, V. G.; Waidyanatha, S.; Devito, M. J.; Eifrid, M. A.; Gibbs, S. T.; Granville, C. A.; Blystone, C. R.	Toxicokinetics of perfluorohexanoic acid (PFHxA), perfluorooctanoic acid (PFOA) and perfluorodecanoic acid (PFDA) in male and female Hsd:Sprague dawley SD rats following intravenous or gavage administration	2019	Xenobiotica. 2020 Jun;50(6):722-732. doi: 10.1080/00498254.2019.1683776. Epub 2019 Nov 7.	Poly- and perfluorinated alkyl substances (PFAS) are environmentally persistent chemicals associated with many adverse health outcomes. The National Toxicology Program evaluated the toxicokinetics (TK) of several PFAS to provide context for toxicologic findings.Plasma TK parameters and tissue (liver, kidney, brain) concentrations are reported for perfluorohexanoic acid (PFHxA), perfluorooctanoic acid (PFOA) or perfluorodecanoic acid (PFDA) after single-dose administration in male and female Hsd:Sprague-Dawley® (SD) rats.Generally, longer Tmax and elimination half-lives, and slower clearance f, were correlated with longer chain length. Male rats administered PFOA had a prolonged half-life compared to females (215 h vs. 2.75), while females had faster clearance and smaller plasma area under the curve (AUC). Females administered PFHxA had a shorter half-life (2 h vs. 9) than males and faster clearance with a smaller plasma AUC, although this was less pronounced than PFOA. There was no sex difference in PFDA half-life. Female rats administered PFDA had a higher plasma AUC/dose than males, and a slower clearance. PFDA had the highest levels in the liver of the PFAS evaluated.Profiling the toxicokinetics of these PFAS allows for comparison among subclasses, and more direct translation of rodent toxicity to human populations.	●	●	●							-		B	B
293	TK	Ehresman, D. J.; Froehlich, J. W.; Olsen, G. W.; Chang, S. C.; Butenhoff, J. L.	Comparison of human whole blood, plasma, and serum matrices for the determination of perfluorooctanesulfonate (PFOS), perfluorooctanoate (PFOA), and other fluorochemicals	2007	Environ Res. 2007 Feb;103(2):176-84. doi: 10.1016/j.envres.2006.06.008. Epub 2006 Aug 8.	Interest in human exposure to perfluorinated acids, including perfluorobutanesulfonate (PFBS), perfluorohexanesulfonate (PFHS), perfluorooctanesulfonate (PFOS), and perfluorooctanoate (PFOA) has led to their measurement in whole blood, plasma and serum. Comparison of measurements in these different blood-based matrices, however, has not been rigorously investigated to allow for across-matrix comparisons. This research evaluated concentrations of PFBS, PFHS, PFOS, and PFOA in whole blood collected in heparin (lithium) and ethylenediamine tetraacetic acid (EDTA), plasma samples collected in heparin and EDTA, and serum (from whole blood allowed to clot). Blood samples were collected from 18 voluntary participants employed at 3M Company. Solid phase extraction methods were used for all analytical sample preparations, and analyses were completed using high-pressure liquid chromatography/tandem mass spectrometry methods. Serum concentrations ranged from: limit of quantitation (LOQ, 5 ng/mL) to 25 ng/mL for PFBS; LOQ (5 ng/mL) to 75 ng/mL for PFHS; LOQ (5 ng/mL) to 880 ng/mL for PFOS; and LOQ (5 or 10 ng/mL) to 7320 ng/mL for PFOA. Values less than the LOQ were not included in the statistical analyses of the mean of the ratios of individual values for the matrices. PFBS was not quantifiable in most samples. Serum to plasma ratios for PFHS, PFOS, and PFOA were 0.0423611111111111 and this ratio was independent of the level of concentrations measured. Serum or plasma to whole blood ratios, regardless of the anticoagulant used, approximated 0.0840277777777778 The difference between plasma and serum and whole blood corresponded to volume displacement by red blood cells, suggesting that the fluorochemicals are not found intracellularly or attached to the red blood cells.	●	●	●	●						-		B	B
294	TK	Eryasa, B.; Grandjean, P.; Nielsen, F.; Valvi, D.; Zmirou-Navier, D.; Sunderland, E.; Weihe, P.; Oulhote, Y.	Physico-chemical properties and gestational diabetes predict transplacental transfer and partitioning of perfluoroalkyl substances	2019	Environ Int. 2019 Sep;130:104874. doi: 10.1016/j.envint.2019.05.068. Epub 2019 Jun 11.	BACKGROUND: Per- and polyfluoroalkyl substances (PFASs) are a growing public health concern. Some longer chain PFASs bioaccumulate and many compounds persist in the environment for long time periods. Recent studies have established their ability to pass through placenta, yet data on the transplacental transfer efficiency and partitioning of short and long chain PFASs in blood matrices are limited.OBJECTIVES: To assess predictors of the partitioning of 17 PFAS compounds detected in the maternal serum, umbilical cord serum and whole cord blood samples from matched mother-newborn pairs from two Faroe Islands cohorts.METHODS: We examined 151 mother-newborn pairs from two successive Faroese birth cohorts. Cord:maternal serum (transplacental transfer) and serum:whole cord blood (blood partitioning) ratios were estimated for 17 PFAS compounds. We also examined the relationships of these ratios with maternal, newborns', and physico-chemical properties using multivariable regression analyses.RESULTS: Moderate to high correlations were observed between maternal and cord serum PFAS concentrations (ρ: 0.41 to 0.95), indicating significant transfer of these compounds from the mother to the fetus. Median transplacental transfer ratios were generally below 1, except for perfluorooctane sulfonamide (FOSA), and ranged between 0.36 for perfluorodecanoate (PFDA) and perfluoroundecanoate (PFUnDA) and 1.21 for FOSA. Most PFASs exhibited a preference to the serum component of the blood, except FOSA and perfluoroheptanoate (PFHpA), with blood partitioning ratios ranging from 0.36 for FOSA to 2.75 for PFUnDA. Both the functional groups and carbon chain length of different PFASs were important predictors of transplacental transfer and blood partitioning. We observed a U-shaped relationship between transplacental transfer ratios and carbon chain length for perfluorocarboxylates and perfluorosulfonates. Importantly, gestational diabetes was also a strong predictor of transplacental transfer ratios, with significantly higher transfer in mothers with gestational diabetes.CONCLUSIONS: Our findings provide a better understanding of the transplacental transfer and blood partitioning of a large number of PFAS compounds. Results elucidate the importance of chemical structure for future risk assessments and choice of appropriate blood matrices for measurement of PFAS compounds.	●	●	●							-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献クラン①抽出	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
295	ADME	Fu, J.; Gao, Y.; Cui, L.; Wang, T.; Liang, Y.; Qu, G.; Yuan, B.; Wang, Y.; Zhang, A.; Jiang, G.	Occurrence, temporal trends, and half-lives of perfluoroalkyl acids (PFAAs) in occupational workers in China	2016	Sci Rep. 2016 Dec 1;6:38039. doi: 10.1038/srep38039.	Paired serum and urine samples were collected from workers in a fluorochemical plant from 2008 to 2012 (n = 302) to investigate the level, temporal trends, and half-lives of PFAAs in workers of a fluorochemical plant. High levels of perfluorohexane sulfonate (PFHxS), perfluorooctanoic acid (PFOA), and perfluorooctanesulfonate (PFOS) were detected in serum with median concentrations of 764, 427, and 1725 ng mL(-1), respectively. The half-lives of PFAAs in workers were estimated by daily clearance rates and annual decline rates of PFAAs in serum by a first-order model. The geometric mean and median value for PFHxS, PFOA, and PFOS were 14.7 and 11.7, 4.1 and 4.0, 32.6 and 21.6 years, respectively, by the daily clearance rates, and they were 3.6, 1.7, and 1.9 years estimated by annual decline rates. The half-lives estimated by the limited clearance route information could be considered as the upper limits for PFAAs, however, the huge difference between two estimated approaches indicated that there were other important elimination pathways of PFAAs other than renal clearance in human. The half-lives estimated by annual decline rates in the present study were the shortest values ever reported, and the intrinsic half-lives might even shorter due to the high levels of ongoing exposure to PFAAs.	●	●	●		●	●				-		1	A	A
296	TK	Fujii, Y.; Niisoe, T.; Harada, K. H.; Uemoto, S.; Ogura, Y.; Takenaka, K.; Koizumi, A.	Toxicokinetics of perfluoroalkyl carboxylic acids with different carbon chain lengths in mice and humans	2015	J Occup Health. 2015;57(1):1-12. doi: 10.1539/joh.14-0136-OA. Epub 2014 Nov 21.	Objectives: Perfluoroalkyl carboxylic acids (PFCAs) consist of analogs with various carbon chain lengths. Their toxicokinetics have remained unexplored except in the case of perfluorooctanoic acid (8 carbon chemicals). This study aimed to investigate the toxicokinetics of PFCAs with six to fourteen carbon atoms (C6 to C14) in mice and humans. Methods: We applied a two-compartment model to mice administered PFCAs intravenously or by gavage. The time courses of the serum concentration and tissue distribution and elimination were evaluated for 24 h after treatment. For human samples, urine from healthy volunteers, bile from patients who underwent biliary drainage, and cerebral spinal fluid (CSF) from brain drainage were collected. Results: The mouse experiment showed that short-chained PFCAs (C6 and C7) were rapidly eliminated in the urine, whereas long-chain PFCAs (C8 to C14) accumulated in the liver and were excreted slowly in feces. Urinary clearance of PFCAs in humans also decreased with increasing alkyl chain lengths, while biliary clearances increased. C9 to C10 had the smallest total clearance for both mice and humans. However, disparities existed in the magnitude of the total clearance between mice and humans. A slightly higher partition ratio (brain/serum) was observed for long-chained PFCAs in mice, but this was not observed in the corresponding partition ratio in humans (CSF/serum). Conclusions: The large sequestration volumes of PFCAs in the liver seem to be attributable to the liver's large binding capacity in both species. This will be useful in evaluating PFCA bioaccumulation in other species.	●	●	●	●						-			B	B
297	TK	Goeden, Helen M; Greene, Christopher W; Jacobus, James A	A transgenerational toxicokinetic model and its use in derivation of Minnesota PFOA water guidance	2019	J Expo Sci Environ Epidemiol. 2019 Mar;29(2):183-195. doi: 10.1038/s41370-018-0110-5. Epub 2019 Jan 10.	Minnesota has been grappling with extensive per- and polyfluoroalkyl substances (PFASs) groundwater contamination since 2002, in a major metropolitan setting. As toxicological information has accumulated for these substances, the public health community has become increasingly aware of critically sensitive populations. The accumulation of some PFAS in women of childbearing age, and the placental and breastmilk transfer to their offspring, require new risk assessment methods to protect public health. The traditional water guidance paradigm is inadequate to address maternal-to-infant transfer of accumulated levels of perfluorooctanoate (PFOA), in particular. Even short exposures during infancy have dramatic impacts on serum levels for many years. In addition, developmental effects are the critical effects anchoring recent risk assessments. In response, the Minnesota Department of Health created an Excel-based model that incorporates chemical-specific properties and exposure parameters for early life stages. Serum levels were assessed in both formula-fed and breastfed infants, with placental transfer in both scenarios. Peak breastfed infant serum levels were 4.4-fold higher than in formula-fed infants, with both of these scenarios producing serum levels in excess of the adult steady-state level. The development and application of this model to PFOA are described.	●	●	●						●	-			A	B
298	TK	Hanssen, Linda; Dudarev, Alexey A; Huber, Sandra; Odland, Jon Øyvind; Nieboer, Evert; Sandanger, Torkjel M	Partition of perfluoroalkyl substances (PFASs) in whole blood and plasma, assessed in maternal and umbilical cord samples from inhabitants of arctic Russia and Uzbekistan	2013	Sci Total Environ. 2013 Mar 1;447:430-7. doi: 10.1016/j.scitotenv.2013.01.029. Epub 2013 Feb 11.	Perfluoroalkyl substances (PFASs) are ubiquitous in the environment world-wide. Our overall objective was to assess the exposure to PFASs experienced by delivering women and their new-borns in the industrial city of Norilsk (arctic Russia) and the rural Aral Sea region of Uzbekistan, with the secondary objective of evaluating the distribution of PFASs between blood cell and plasma fractions. Six PFASs were detected in every sample from Norilsk city with the plasma concentration sequence of: PFOS≫PFOA>PFNA>FOSA>PFHxS>PFUnDA. In the Uzbekistani samples, only PFOS was reported above the MDL (0.08 ng/mL). The median plasma concentrations of PFOS of 11.0 ng/mL for the Norilsk mothers was comparable to that reported for western countries, while that for Uzbekistan was considerably lower (0.23 ng/mL). Apparent increases in the maternal-cord concentration ratios for both whole blood and plasma were evident with the length of the carbon chain for both the carboxylate and the sulfonate PFASs. The median value of this ratio for FOSA in plasma was the lowest, while that for whole blood was the highest. Other than for FOSA, the observed plasma-whole blood concentration ratios for maternal and umbilical cord blood were consistent with a priori calculations using appropriate packed cell and plasma volumes for neonates and pregnant women at term. Clearly FOSA favored whole blood, and acid-base equilibrium calculations suggested that the resonance-stabilized sulfonamidate ion resides in the blood cell fraction. Thus for PFASs and related compounds with pK values with magnitudes comparable to physiological pH, it is pertinent to measure the cell-associated fraction (separately or as whole blood). Our study illustrates that consideration of both the physico-chemical properties of the contaminants and the physiological attributes of blood matrices were helpful in the interpretation of our findings.	●	●	●	●						-			B	B
299	ADME	Harada, Kouji; Inoue, Kayoko; Morikawa, Akiko; Yoshinaga, Takeo; Saito, Norimitsu; Koizumi, Akio	Renal clearance of perfluorooctane sulfonate and perfluorooctanoate in humans and their species-specific excretion	2005	Environ Res. 2005 Oct;99(2):253-61. doi: 10.1016/j.envres.2004.12.003. Epub 2005 Jan 18.	Perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) are detected in the environment, as well as more specifically in wildlife and humans. However, the toxicokinetic aspects of perfluorochemicals in humans are unclear. In this study, we measured concentrations of PFOA and PFOS in subjects who had lived in Kyoto city for more than 10 years. The serum concentrations of PFOA and PFOS were higher in females who menstruated than those who did not menstruation (P<0.01), but in males this did not change by age; the levels in females reached those in males at an age of 60 years. We then determined the renal clearances of PFOA and PFOS in young (20-40 years old, N=5 for each sex) and old (60 years old, N=5 for each sex) subjects of both sexes. All young females were menstruating, while all old females were not. The renal clearances were 10(-5)-fold smaller than the glomerular filtration rate in humans, suggesting the absence of active excretion in human kidneys. The renal clearances of PFOA and PFOS were approximately one-fifth of the total clearance based on their serum half-lives, assuming a one-compartment model. The sex differences in renal clearance that have been reported in rats and Japanese macaques were not found in our human subjects. We tried to build a one-compartment pharmacokinetic model using the reported half-lives in human. The model was simple but could predict the serum concentrations in both males and females fairly well. We therefore suggest that an internal dose approach using a pharmacokinetic model should be taken because of the large species differences in kinetics that exist for PFOA and PFOS.	●	●	●	●	●	●			●	-		1	A	A
300	ADME	Harada, K. H.; Hashida, S.; Kaneko, T.; Takenaka, K.; Minata, M.; Inoue, K.; Saito, N.; Koizumi, A.	Biliary excretion and cerebrospinal fluid partition of perfluorooctanoate and perfluorooctane sulfonate in humans	2007	Environ Toxicol Pharmacol. 2007 Sep;24(2):134-9. doi: 10.1016/j.etap.2007.04.003. Epub 2007 May 4.	Perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) are detected in the environment and, more specifically, in wildlife and humans. The large variation in the reported biological half-lives for PFOA and PFOS has remained unexplored. In this study, we aimed to evaluate their partition from serum to bile and cerebrospinal fluid (CSF) in humans. Four pairs of serum and bile, and 7 pairs of serum and CSF were donated by patients. In considering biliary excretion, the median concentrations of PFOA and PFOS in serum samples were 3.8 and 23.2ng/mL, respectively, whereas those in bile samples were 1 and 27.9ng/mL, respectively. The median ratio of PFOS concentrations (bile/serum: 0.60) was significantly higher than that for PFOA, 0.21 (p<0.01). Biliary excretion rates for PFOA and PFOS in the present study subjects were estimated as 1.06 and 2.98mL/kg/day, respectively, which is significantly higher than serum clearances via urine in humans and might represent a major excretion route. Biliary reabsorption rates of PFOA and PFOS were estimated to be 0.89 and 0.97, respectively. In considering partition into the cerebrospinal fluid, the median concentrations of PFOA and PFOS in serum samples were 2.6 and 18.4ng/mL, respectively, whereas those in CSF samples were 0.06 and 0.10ng/mL, respectively. The median ratio of PFOS concentrations (CSF/serum: 9.1 (×10(-3))) was comparable to that of PFOA, 17.6 (×10(-3)), suggesting that PFOA and PFOS cannot pass through the blood-brain barrier freely. In conclusion, the biliary excretion of these compounds was comparable in both rats and humans and the long half-lives in humans might be attributable to low levels of excretion in urine and high biliary reabsorption rates.	●	●	●	●	●	●			●	-		1	A	A
301	TK	Haug, L. S.; Huber, S.; Becher, G.; Thomsen, C.	Characterisation of human exposure pathways to perfluorinated compounds--comparing exposure estimates with biomarkers of exposure	2011	Environ Int. 2011 May;37(4):687-93. doi: 10.1016/j.envint.2011.01.011. Epub 2011 Feb 18.	Commercially used per- and polyfluorinated compounds (PFCs) have been widely detected in humans, but the sources of human exposure are not fully characterized. The objectives of this study were to assess the relative importance of different exposure pathways of PFCs in a group of Norwegians and compare estimated intakes with internal doses obtained through biomonitoring. Individual PFC intakes from multiple exposure sources for a study group of 41 Norwegian women were estimated using measured PFC concentrations in indoor air and house dust as well as information from food frequency questionnaires and PFC concentrations in Norwegian food. Food was generally the major exposure source, representing 67-84% of the median total intake for PFOA and 88-99% for PFOS using different dust ingestion rates and biotransformation factors of precursor' compounds. However, on an individual basis, the indoor environment accounted for up to around 0.5 of the total intake for several women. Significant positive associations between concentrations of PFCs in house dust and the corresponding serum concentrations underline the importance of indoor environment as an exposure pathway for PFCs. For breast-fed infants, breast milk was calculated to be the single most important source to PFCs by far. The estimated intakes were confirmed by comparing serum concentrations of PFOA and PFOS calculated using PK models, with the corresponding concentrations measured in serum. Even though food in general is the major source of exposure for PFCs, the indoor environment may be an important contributor to human exposure. This study provides valuable knowledge for risk assessment of PFCs and control strategies.	●	●	●							-			B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献ランク①	文献ランク②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
302	TK	Huang, MC; Dzierlenga, AL; Robinson, VG; Waidyanatha, S; Devito, MJ; Eifrid, MA; Granville, CA; Gibbs, ST; Blystone, CR.	Toxicokinetics of perfluorobutane sulfonate (PFBS), perfluorohexane-1-sulphonic acid (PFHxS), and perfluorooctane sulfonic acid (PFOS) in male and female Hsd:Sprague Dawley SD rats after intravenous and gavage administration	2019	Toxicology Reports. 2019 Jun 28;6:645-655. doi: 10.1016/j.toxrep.2019.06.016. eCollection 2019.	Perfluorinated alkyl substances (PFAS) are persistent contaminants that have been detected in the environment and in humans. With the PFAS chemical class, there are perfluorinated alkyl acids, many of which have been associated with certain toxicities. Because toxicity testing cannot feasibly be conducted for each individual PFAS, the National Toxicology Program (NTP) designed studies to compare toxicities across different subclasses of PFAS and across PFAS of different chain lengths to better understand the structure-toxicity relationship. Pharmacokinetic studies were conducted in parallel to these toxicity studies to facilitate comparisons across PFAS and to provide context for human relevance. Here, the toxicokinetic parameters of perfluorobutane sulfonate (PFBS), perfluorohexane-1-sulphonic acid (PFHxS), or perfluorooctane sulfonate (PFOS) after a single intravenous or gavage administration in male and female Hsd:Sprague-Dawley rats are reported. Concentrations of these PFAS were measured in the liver, kidney, and brain. Plasma half-life increased with longer chain length after gavage administration: PFBS- males averaged 3.3 h, females 1.3 h; PFHxS- males averaged 16.3 days, females 2.1 days; PFOS- males and females averaged ˜ 20 days. There were dose-dependent changes in clearance and systemic exposure for all administered chemicals and the direction of change was different in PFOS compared to the others. Liver:plasma ratios of PFOS were the highest followed by PFHxS and PFBS, while brain:plasma ratios were low in all three sulfonates. Sex differences in plasma half-life and tissue distribution were observed for PFBS and PFHxS, but not PFOS. These data provide a direct comparison of the kinetics of three different perfluoroalkyl sulfonic acids and allow for the contextualization of toxicity data in rats for human risk assessment of this chemical class.	●	●	●						●	-		B	B
303	TK	Inoue, K.; Okada, F.; Ito, R.; Kato, S.; Sasaki, S.; Nakajima, S.; Uno, A.; Saijo, Y.; Sata, F.; Yoshimura, Y.; Kishi, R.; Nakazawa, H.	Perfluorooctane sulfonate (PFOS) and related perfluorinated compounds in human maternal and cord blood samples: assessment of PFOS exposure in a susceptible population during pregnancy	2004	Environ Health Perspect. 2004 Aug;112(11):1204-7. doi: 10.1289/ehp.6864.	Fluorinated organic compounds (FOCs), such as perfluorooctane sulfonate (PFOS), perfluoro-octanoate (PFOA), and perfluorooctane sulfonylamide (PFOSA), are widely used in the manufacture of plastic, electronics, textile, and construction material in the apparel, leather, and upholstery industries. FOCs have been detected in human blood samples. Studies have indicated that FOCs may be detrimental to rodent development possibly by affecting thyroid hormone levels. In the present study, we determined the concentrations of FOCs in maternal and cord blood samples. Pregnant women 17-37 years of age were enrolled as subjects. FOCs in 15 pairs of maternal and cord blood samples were analyzed by liquid chromatography-electrospray mass spectrometry coupled with online extraction. The limits of quantification of PFOS, PFOA, and PFOSA in human plasma or serum were 0.5, 0.5, and 1 ng/mL, respectively. The method enables the precise determination of FOCs and can be applied to the detection of FOCs in human blood samples for monitoring human exposure. PFOS concentrations in maternal samples ranged from 4.9 to 17.6 ng/mL, whereas those in fetal samples ranged from 1.6 to 5.3 ng/mL. In contrast, PFOSA was not detected in fetal or maternal samples, whereas PFOA was detected only in maternal samples (range, < 0.5 to 2.3 ng/mL, 4 of 15). Our results revealed a high correlation between PFOS concentrations in maternal and cord blood (r2 = 0.876). However, we did not find any significant correlations between PFOS concentration in maternal and cord blood samples and age bracket, birth weight, or levels of thyroid-stimulating hormone or free thyroxine. Our study revealed that human fetuses in Japan may be exposed to relatively high levels of FOCs. Further investigation is required to determine the postnatal effects of fetal exposure to FOCs	●	●	●	●	●		●			-		B	B
304	TK	Iwabuchi, K.; Senzaki, N.; Mazawa, D.; Sato, I.; Hara, M.; Ueda, F.; Liu, W.; Tsuda, S.	Tissue toxicokinetics of perfluoro compounds with single and chronic low doses in male rats	2017	J Toxicol Sci. 2017;42(3):301-317. doi: 10.2131/jts.42.301.	To examine the kinetics of low doses of perfluoro compounds (PFCs), we administered perfluorohexanoic acid (C6A), perfluorooctanoic acid (C8A), perfluorononanoic acid (C9A) and perfluorooctane sulfonate (C8S) with a single oral dose (50-100 µg/kg BW), and in drinking water at 1, 5, and 25 µg/L for one and three months to male rats; and examined the distribution in the brain, heart, liver, spleen, kidney, whole blood and serum. C6A was very rapidly absorbed, distributed and eliminated from the tissues with nearly the same tissue t1/2 of 44595 hr. Considering serum Vd, and the tissue delivery, C6A was mainly in the serum with the lowest delivery to the brain; and no tissue accumulation was observed in the chronic studies as estimated from the single dose study. For the other PFCs, the body seemed to be an assortment of independent one-compartments with a longer elimination t1/2 for the liver than the serum. The concentration ratio of liver/serum increased gradually from C0 to a steady state. The high binding capacity of plasma protein may be the reason for the unusual kinetics, with only a very small fraction of free PFCs moving gradually to the liver. Although the tissue specific distribution was time dependent and different among the PFCs, the Vd and ke of each tissue were constant throughout the study. The possibility of extremely high C6A accumulation in the human brain and liver was suggested, by comparing the steady state tissue concentration of this study with the human data reported by Pérez et al. (2013).	●	●	●	●						-		B	B
305	ADME	Jin, H.; Zhang, Y.; Jiang, W.; Zhu, L.; Martin, J. W.	Isomer-Specific Distribution of Perfluoroalkyl Substances in Blood	2016	Environ Sci Technol. 2016 Jul 19;50(14):7808-15. doi: 10.1021/acs.est.6b01698. Epub 2016 Jun 23.	Perfluoroalkyl substances (PFASs) such as perfluorohexanesulfonate (PFHxS), perfluorooctanoate (PFOA), perfluorooctanesulfonate (PFOS) and PFOS-precursors are routinely measured in human plasma and serum, but their relative abundance in the blood cell fraction has not been carefully examined, particularly at the isomer-specific level. Human plasma and whole blood were collected and partitioning behaviors of PFASs and their isomers between plasma and blood cells were investigated. In human samples, mass fraction in plasma (Fp) for PFASs increased among perfluoroalkyl carboxylates as the carbon chain length increased from C6 (mean 0.24) to C11 (0.87), indicating preference for the plasma fraction with increasing chain length. However, among perfluoroalkyl sulfonates, PFHxS (mean 0.87) had a slightly higher Fp than PFOS (0.85). In vitro assays with spiked Sprague-Dawley rat blood were also conducted, and the results showed that PFOS-precursors had lower Fp values than perfluoroalkyl acids, with perfluoroctanesulfonamide having the lowest Fp (mean 0.24). Consistently, linear isomers of PFOS and PFOS-precursors had lower mean Fp than their corresponding total branched isomers. Multiplying by a factor of 2 is not a reasonable method to convert from whole blood to plasma PFAS concentrations, and current ratios could be used as more accurate conversion factors.	●	●	●	●						-	1	A	A
306	ADME	Kim, S. J.; Heo, S. H.; Lee, D. S.; Hwang, I. G.; Lee, Y. B.; Cho, H. Y.	Gender differences in pharmacokinetics and tissue distribution of 3 perfluoroalkyl and polyfluoroalkyl substances in rats	2016	Food Chem Toxicol. 2016 Nov;97:243-255. doi: 10.1016/j.fct.2016.09.017. Epub 2016 Sep 13.	The aim of this study was to confirm and investigate the gender differences in pharmacokinetic (PK) characteristics and tissue distribution of 3 perfluoroalkyl and polyfluoroalkyl substances (PFASs) consisted of perfluorooctanoic acid (PFOA), perfluorooctanesulfonic acid (PFOS), and perfluorohexane sulfonic acid (PFHxS) in both male and female rats. For this study, a simultaneous determination method of the 3 PFASs in rat plasma and tissues was developed and validated using a UPLC-MS/MS system. The PK parameters after a single oral or intravenous administration of the 3 PFASs in both rats were calculated using WinNonlin(®) software. The mean half-life of the 3 PFASs in female and male rats was in the range of 0.15-0.19 and 1.6-1.8 days for PFOA, 23.5-24.8 and 26.4-28.7 days for PFOS, and 0.9-1.7 and 20.7-26.9 days for PFHxS, respectively. The 3 PFASs were highly distributed in the liver and kidney. These results suggest that there are gender differences in the PKs for PFOA and PFHxS in rats, whereas the PFOS represented no significant gender differences except the Kp value of liver. The validated simultaneous determination method of the 3 PFASs was also within the accepted criteria of the international guidance.	●	●	●	●			●		●	-		B	A
307	TK	Kudo, Naomi; Katakura, Masanori; Sato, Yasunori; Kawashima, Yoichi	Sex hormone-regulated renal transport of perfluorooctanoic acid	2002	Chem Biol Interact. 2002 Mar 20;139(3):301-16. doi: 10.1016/s0009-2797(02)00006-6.	The biological half-life (t1/2) of perfluorooctanoic acid (PFOA) in male rats is 70 times longer than that in female rats. The difference is mainly due to the difference in renal clearance (CL(R)), which was significantly reduced by probenecid, suggesting that PFOA is excreted by organic anion transporter(s). Castration of male rats caused a 14-fold increase in the CL(R) of PFOA, which made it comparable with that of female rats. The elevated PFOA CL(R) in castrated males was reduced by treating them with testosterone. Treatment of male rats with estradiol increased the CL(R) of PFOA. In female rats, ovariectomy caused a significant increase in CL(R) of PFOA, which was reduced by estradiol treatment. Treatments of female rats with testosterone reduced the CL(R) of PFOA as observed in castrated male rats. To identify the transporter molecules that are responsible for PFOA transport in rat kidney, renal mRNA levels of organic anion transporter 1 (OAT1), OAT2, OAT3, organic anion transporting polypeptide 1 (oatp1), oatp2 and kidney specific organic anion transporter (OAT-K) were determined in male and female rats under various hormonal states and compared with the CL(R) of PFOA. The level of OAT2 mRNA in male rats was only 13% that in female rats. Castration or estradiol treatment increased the level of OAT2 mRNA whereas treatment of castrated male rats with testosterone reduced it. In contrast to OAT2, mRNA levels of both oatp1 and OAT-K were significantly higher in male rats compared with female rats. Castration or estradiol treatment caused a reduction in the levels of mRNA of oatp1 and OAT-K in male rats. Ovariectomy of female rats significantly increased the level of OAT3 mRNA. Multiple regression analysis suggests that the change in the CL(R) of PFOA is, at least in part, due to altered expression of OAT2 and OAT3.	●	●	●	●					●	-		B	B
308	TK	Luebker, D. J.; Hansen, K. J.; Bass, N. M.; Butenhoff, J. L.; Seacat, A. M.	Interactions of fluorochemicals with rat liver fatty acid-binding protein	2002	Toxicology. 2002 Jul 15;176(3):175-85. doi: 10.1016/s0300-483x(02)00081-1.	Liver-fatty acid binding protein (L-FABP) is an abundant intracellular lipid-carrier protein. The hypothesis that perfluorooctanesulfonate (PFOS), perfluorooctanoate (PFOA), and certain related perfluorooctanesulfonamide-based fluorochemicals (PFOSAs) can interfere with the binding affinity of L-FABP for fatty acids was tested. The relative effectiveness of PFOA, PFOS, N-ethylperfluorooctanesulfonamide (N-EtFOSA), N-ethylperfluorooctanesulfonamido ethanol (N-EtFOSE), and of the strong peroxisome proliferator Wyeth-14643 (WY) to inhibit 11-(5-dimethylaminonapthalenesulphonyl)-undecanoic acid (DAUDA) binding to-L-FABP was determined. The dissociation constant (Kd) of the DAUDA-L-FABP complex was 0.47 nM. PFOS exhibited the highest level of inhibition of DAUDA-L-FABP binding in the competitive binding assays, followed by N-EtFOSA, WY, and, with equal IC(50)s, N-EtFOSE and PFOA. The in vitro data presented in this study support the hypothesis that these fluorochemicals may interfere with the binding of fatty acids or other endogenous ligands to L-FABP. Furthermore, this work provides evidence to support the hypothesis that displacement of endogenous ligands from L-FABP may contribute to toxicity in rodents fed these fluorochemicals.	●	●	●	●	●	●				-		A	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
309	TK	Macmanus-Spencer, L. A.; Tse, M. L.; Hebert, P. C.; Bischel, H. N.; Luthy, R. G.	Binding of perfluorocarboxylates to serum albumin: a comparison of analytical methods	2010	Anal Chem. 2010 Feb 1;82(3):974-81. doi: 10.1021/ac902238u.	Perfluorochemicals are globally pervasive contaminants that are persistent, bioaccumulative, and toxic. Perfluorocarboxylic acids (PFCAs) with 44786 carbons accumulate in the liver and blood of aquatic organisms; PFCA-protein interactions may explain this accumulation pattern. Here, the interactions between PFCAs with 44784 carbons and serum albumin are examined using three experimental approaches: surface tension titrations, (19)F NMR spectroscopy, and fluorescence spectroscopy. Surface tension titrations indicate complex formation at high (mM) PFCA concentrations. Secondary association constants ranging from 10(2) to 10(4) M(-1) were determined from (19)F NMR titrations at high PFCA:albumin mole ratios. Fluorescence measurements indicate that PFCA-albumin interactions alter the protein conformation at low PFCA:albumin mole ratios (up to 5:1) and suggest two binding classes with association constants around 10(5) and 10(2) M(-1). While (19)F NMR and fluorescence provide both qualitative and quantitative information about PFCA-albumin interactions, surface tension provides only qualitative information. Limitations associated with instrumentation and methods require high PFCA concentrations in both surface tension and (19)F NMR experiments; in contrast, fluorescence allows for analysis of a wider range of PFCA concentrations and PFCA:albumin mole ratios. Results from this study indicate that fluorescence, though an indirect method, offers a more comprehensive picture of the nature of PFCA-albumin interactions.	●	●	●							-		B	B
310	TK	Pizzurro, D. M.; Seeley, M.; Kerper, L. E.; Beck, B. D.	Interspecies differences in perfluoroalkyl substances (PFAS) toxicokinetics and application to health-based criteria [Review]	2019	Regul Toxicol Pharmacol. 2019 Aug;106:239-250. doi: 10.1016/j.yrtph.2019.05.008. Epub 2019 May 9.	Toxicokinetics are important for extrapolating health effects and effect levels observed in laboratory animals to humans for purposes of establishing health-based criteria. We conducted a comprehensive review of key absorption, distribution, metabolism, and excretion (ADME) parameters across different mammalian species for five perfluoroalkyl substances (PFAS) and discussed how these data can be used to inform human health risk assessment of these substances. Our analysis revealed several notable differences among the different PFAS regarding species- and substance-specific tissue partitioning, half-life, and transfer to developing offspring via the placenta or lactation, as well as highlighted data gaps for certain substances. We incorporated these observations in an analysis of whether health-based values for specific PFAS can be applied to other PFAS of differing chain length or toxicological mode of action. Overall, our analysis provides one of the first syntheses of available empirical PFAS toxicokinetic data to facilitate interpreting human relevance of animal study findings and developing health-based criteria for PFAS from such studies.	●	●	●							-		B	B
311	TK	Porpora, M. G.; Lucchini, R.; Aballe, A.; Ingelido, A. M.; Valentini, S.; Fuggetta, E.; Cardi, V.; Ticino, A.; Marra, V.; Fulgenzi, A. R.; Felip, E. D.	Placental transfer of persistent organic pollutants: a preliminary study on mother-newborn pairs	2013	Int J Environ Res Public Health. 2013 Feb 7;10(2):699-711. doi: 10.3390/ijerph10020699.	The aim of this study was to characterize the placental transfer of some environmental pollutants, and to explore the possibility of quantitatively predicting in utero exposure to these contaminants from concentrations assessed in maternal blood. Levels of toxic substances such as pesticides (p,p'-DDE, β-HCH, and HCB), polychlorinated biphenyls (PCBs), perfluorooctane sulfonate (PFOS), and perfluorooctanoic acid (PFOA) were determined in serum samples of 38 pregnant women living in Rome and in samples of cord blood from their respective newborns. The study was carried out in the years 2008-2009. PCB mean concentrations in maternal serum and cord serum ranged from 0.058 to 0.30, and from 0.018 to 0.064 ng/g · fw respectively. Arithmetic means of PFOS and PFOA concentrations in mothers and newborns were 3.2 and 1.4 ng/g · fw, and 2.9 and 1.6 ng/g · fw. A strong correlation was observed between concentrations in the maternal and the foetal compartment for PFOS (Spearman r = 0.74, p < 0.001), PFOA (Spearman r = 0.70, p < 0.001), PCB 153 (Spearman r = 0.60, p < 0.001), HCB (Spearman r = 0.68, p < 0.001), PCB 180 (Spearman r = 0.55, p = 0.0012), and p,p'-DDE (Spearman r = 0.53, p =0.0099). A weak correlation (p < 0.1) was observed for PCBs 118 and 138	●	●	●	●						-		B	B
312	ADME	Seals, Ryan; Bartell, Scott M; Steenland, Kyle	Accumulation and clearance of perfluorooctanoic acid (PFOA) in current and former residents of an exposed community	2011	Environ Health Perspect. 2011 Jan;119(1):119-24. doi: 10.1289/ehp.1002346. Epub 2010 Sep 22.	BACKGROUND: Perfluorooctanoic acid (PFOA) is a perfluoroalkyl acid found in > 99% of Americans. Its health effects are unknown. Prior estimates of serum half-life range from 2.3 to 3.8 years. OBJECTIVES: We assessed the impact of years of residence and years since residing in the study area on serum PFOA concentration in a sample of current and former residents who were exposed to PFOA emissions from an industrial facility in six water districts in West Virginia and Ohio. METHODS: Serum samples and questionnaires, including residential history, were collected in 2005-2006. We modeled log serum PFOA (nanograms per milliliter) for current residents as a function of years of residence in a water district, adjusted for a variety of factors. We modeled the half-life in former residents who lived in two water districts with high exposure levels using a two-segment log-linear spline. RESULTS: We modeled serum PFOA concentration in 17,516 current residents as a function of years of residence (R2 = 0.68). Years of residence was significantly associated with PFOA concentration (1% increase in serum PFOA/year of residence), with significant heterogeneity by water district. Half-life was estimated in two water districts comprising a total of 1,573 individuals. For the participants included in our analyses, we found that years since residing in a water district was significantly associated with serum PFOA, which yielded half-lives of 2.9 and 8.5 years for water districts with higher and lower exposure levels, respectively. CONCLUSION: Years of residence in an exposed water district is positively associated with observed serum PFOA in 2005-2006. Differences in serum clearance rate between low- and high-exposure water districts suggest a possible concentration-dependent or time-dependent clearance process or inadequate adjustment for background exposures.	●	●	●	●		●				-		B	A
313	ADME	Thompson, J.; Lorber, M.; Toms, L. M.; Kato, K.; Calafat, A. M.; Mueller, J. F.	Use of simple pharmacokinetic modeling to characterize exposure of Australians to perfluorooctanoic acid and perfluorooctane sulfonic acid	2010	Environ Int. 2010 May;36(4):390-397. doi: 10.1016/j.envint.2010.02.008. Epub 2010 Mar 16.	Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS) have been used for a variety of applications including fluoropolymer processing, fire-fighting foams and surface treatments since the 1950s. Both PFOS and PFOA are polyfluoroalkyl chemicals (PFCs), man-made compounds that are persistent in the environment and humans; some PFCs have shown adverse effects in laboratory animals. Here we describe the application of a simple one compartment pharmacokinetic model to estimate total intakes of PFOA and PFOS for the general population of urban areas on the east coast of Australia. Key parameters for this model include the elimination rate constants and the volume of distribution within the body. A volume of distribution was calibrated for PFOA to a value of 170ml/kgbw using data from two communities in the United States where the residents' serum concentrations could be assumed to result primarily from a known and characterized source, drinking water contaminated with PFOA by a single fluoropolymer manufacturing facility. For PFOS, a value of 230ml/kgbw was used, based on adjustment of the PFOA value. Applying measured Australian serum data to the model gave mean+/-standard deviation intake estimates of PFOA of 1.6+/-0.3ng/kgbw/day for males and females >12years of age combined based on samples collected in 2002-2003 and 1.3+/-0.2ng/kg bw/day based on samples collected in 2006-2007. Mean intakes of PFOS were 2.7+/-0.5ng/kgbw/day for males and females >12years of age combined based on samples collected in 2002-2003, and 2.4+/-0.5ng/kgbw/day for the 2006-2007 samples. ANOVA analysis was run for PFOA intake and demonstrated significant differences by age group (p=0.03), sex (p=0.001) and date of collection (p<0.001). Estimated intake rates were highest in those aged >60years, higher in males compared to females, and higher in 2002-2003 compared to 2006-2007. The same results were seen for PFOS intake with significant differences by age group (p<0.001), sex (p=0.001) and date of collection (p=0.016).	●	●	●	●	●	●				-	1	A	A
314	ADME	Thomsen, C.; Haug, L. S.; Stigum, H.; Froshaug, M.,ay; Broadwell, S. L.; Becher, G.	Changes in concentrations of perfluorinated compounds, polybrominated diphenyl ethers, and polychlorinated biphenyls in Norwegian breast-milk during twelve months of lactation	2000	Environ Sci Technol. 2010 Dec 15;44(24):9550-6. doi: 10.1021/es1021922. Epub 2010 Nov 23.	At present, scientific knowledge on depuration rates of persistent organic pollutants (POPs) is limited and the previous assumptions of considerable reduction of body burdens through breast-feeding have recently been challenged. We therefore studied elimination rates of important POPs in nine Norwegian primiparous mothers and one mother breast-feeding her second child by collecting breast-milk samples (n = 70) monthly from about two weeks to up to twelve months after birth. Perfluorinated compounds (PFCs), polybrominated diphenyl ethers (PBDEs), hexabromocyclododecane (HBCD), and polychlorinated biphenyls (PCBs) were determined in the breast-milk samples. Linear mixed effect models were established for selected compounds, and significant decreases in the range of 1.2-4.7% in breast-milk concentrations per month were observed for a wide range of PCBs and PBDEs. For the first time, depuration rates for perfluorooctylsulfonate (PFOS) and perfluorooctanoic acid (PFOA) are presented, being 3.8 and 7.8% per month, respectively (p < 0.05). The relative amount of the branched PFOS isomers in the breast-milk samples was 18% on average (range 6-36%, RSD 30%). There were no significant differences in isomer pattern between the mothers, or changes during the lactation period. After a year of nursing the breast-milk concentrations of PFCs, PBDEs, and PCBs were reduced by 15-94%.	●	●	●	●	●	●			●	-	1	A	A
315	TK	Weaver, Y. M.; Ehresman, D. J.; Butenhoff, J. L.; Hagenbuch, B.	Roles of rat renal organic anion transporters in transporting perfluorinated carboxylates with different chain lengths	2010	Toxicol Sci. 2010 Feb;113(2):305-14. doi: 10.1093/toxsci/kfp275. Epub 2009 Nov 13.	Perfluorinated carboxylates (PFCAs) are generally stable to metabolic and environmental degradation and have been found at low concentrations in environmental and biological samples. Renal clearance of PFCAs depends on chain length, species, and, in some cases, gender within species. While perfluoroheptanoate (C7) is almost completely eliminated renally in both male and female rats, renal clearance of perfluorooctanoate (C8) and perfluorononanoate (C9) is much higher in female rats. Perfluorodecanoate (C10) mainly accumulates in the liver for both genders. Therefore, we tested whether PFCAs with different chain lengths are substrates of rat renal transporters with gender-specific expression patterns. Inhibition of uptake of model substrates was measured for the basolateral organic anion transporter (Oat)1 and Oat3 and the apical Oat2, organic anion transporting polypeptide (Oatp)1a1, and Urat1 with 10microM PFCAs with chain lengths from 2 to 18 (C2-C18) carbons. Perfluorohexanoate (C6), C7, and C8 inhibited Oat1-mediated p-aminohippurate transport, with C7 being the strongest inhibitor. C8 and C9 were the strongest inhibitors for Oat3-mediated estrone-3-sulfate transport, while Oatp1a1-mediated estradiol-17beta-glucuronide uptake was inhibited by C9, C10, and perfluoroundecanoate (C11), with C10 giving the strongest inhibition. No strong inhibitors were found for Oat2 or Urat1. Kinetic analysis was performed for the strongest inhibitors. Oat1 transported C7 and C8 with K(m) values of 50.5 and 43.2microM, respectively. Oat3 transported C8 and C9 with K(m) values of 65.7 and 174.5microM, respectively. Oatp1a1-mediated transport yielded K(m) values of 126.4 (C8), 20.5 (C9), and 28.5microM (C10). These results suggest that Oat1 and Oat3 are involved in renal secretion of C7-C9, while Oatp1a1 can contribute to the reabsorption of C8 through C10, with highest affinities for C9 and C10.	●	●	●	●						-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献①ラン	文献②ラン
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
316	ADME	Worley, R. R.; Moore, S. M.; Tierney, B. C.; Ye, X.; Calafat, A. M.; Campbell, S.; Woudneh, M. B.; Fisher, J.	Per- and polyfluoroalkyl substances in human serum and urine samples from a residentially exposed community	2017	Environ Int. 2017 Sep;106:135-143. doi: 10.1016/j.envint.2017.06.007. Epub 2017 Jun 20.	BACKGROUND: Per- and polyfluoroalkyl substances (PFAS) are considered chemicals of emerging concern, in part due to their environmental and biological persistence and the potential for widespread human exposure. In 2007, a PFAS manufacturer near Decatur, Alabama notified the United States Environmental Protection Agency (EPA) it had discharged PFAS into a wastewater treatment plant, resulting in environmental contamination and potential exposures to the local community.OBJECTIVES: To characterize PFAS exposure over time, the Agency for Toxic Substances and Disease Registry (ATSDR) collected blood and urine samples from local residents.METHODS: Eight PFAS were measured in serum in 2010 (n=153). Eleven PFAS were measured in serum, and five PFAS were measured in urine (n=45) from some of the same residents in 2016 Serum concentrations were compared to nationally representative data and change in serum concentration over time was evaluated. Biological half-lives were estimated for perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), and perfluorohexane sulfonic acid (PFHxS) using a one-compartment pharmacokinetic model.RESULTS: In 2010 and 2016, geometric mean PFOA and PFOS serum concentrations were elevated in participants compared to the general U.S.POPULATION: In 2016, the geometric mean PFHxS serum concentration was elevated compared to the general U.S. POPULATION: Geometric mean serum concentrations of PFOA, PFOS, and perfluorononanoic acid (PFNA) were significantly (p≤0.0001) lower (49%, 53%, and 58%, respectively) in 2016 compared to 2010 Half-lives for PFOA, PFOS, and PFHxS were estimated to be 3.9, 3.3, and 15.5years, respectively. Concentrations of PFOA in serum and urine were highly correlated (r=0.75) in males.CONCLUSIONS: Serum concentrations of some PFAS are decreasing in this residentially exposed community, but remain elevated compared to the U.S. general population.	●	●	●	●					●	-		B	A
317	TK	Yang, Ching-Hui; Glover, Kyle P; Han, Xing	Characterization of cellular uptake of perfluorooctanoate via organic anion-transporting polypeptide 1A2, organic anion transporter 4, and urate transporter 1 for their potential roles in mediating human renal reabsorption of perfluorocarboxylates	2010	Toxicol Sci. 2010 Oct;117(2):294-302. doi: 10.1093/toxsci/kfq219. Epub 2010 Jul 16.	It has been hypothesized that human renal apical membrane transporters play a key role in human renal reabsorption of perfluorooctanoate (PFO), which contributes to the long half-life of PFO in humans. In the present study, PFO uptake kinetics of human organic anion-transporting polypeptide (OATP) 1A2, organic anion transporter (OAT) 4, and urate transporter 1 (URAT1) in stably transfected cell lines was investigated. OAT4 and URAT1, but not OATP1A2, were shown to mediate saturable PFO cellular uptake. OAT4-mediated PFO uptake was stimulated by a low extracellular pH, which was evidenced as a lower Michaelis constant (K(m)) at pH 6 (172.3 ± 45.9μM) than that at pH 7.4 (310.3 ± 30.2μM). URAT1-mediated PFO uptake was greatly enhanced by an outward Cl(-) gradient, and its K(m) value was determined to be 64.1 ± 30.5μM in the absence of extracellular Cl(-). The inhibition of OATP1A2- or OAT4-mediated estrone-3-sulfate uptake or URAT1-mediated urate uptake has been compared for linear perfluorocarboxylates (PFCs) with carbon chain lengths from 4 to 12. A clear chain length-dependent inhibition was observed, suggesting that PFCs in general are substrates of OAT4 and URAT1 but with different levels of affinities to the transporters depending on their chain length. Our results suggest that OAT4 and URAT1 are key transporters in renal reabsorption of PFCs in humans and, as a result, may contribute significantly to the long half-life of PFO in humans.	●	●	●	●		●				-		A	B
318	TK	Zhang, L.; Ren, X. M.; Guo, L. H.	Structure-based investigation on the interaction of perfluorinated compounds with human liver fatty acid binding protein	2013	Environ Sci Technol. 2013 Oct 1;47(19):11293-301. doi: 10.1021/es4026722. Epub 2013 Sep 20.	Perfluorinated compounds (PFCs) are known to accumulate in liver and induce hepatotoxicity on experimental animals. Liver fatty acid binding protein (L-FABP) is expressed highly in hepatocytes and binds fatty acids. PFCs may bind with FABP and change their ADME and toxicity profile. In the present study, the binding interaction of 17 structurally diverse PFCs with human L-FABP was investigated to assess their potential disruption effect on fatty acid binding. The binding affinity of twelve perfluorinated carboxylic acids (PFCAs), as determined by fluorescence displacement assay, increased significantly with their carbon number from 4 to 11, and decreased slightly when the number was over 11 The three perfluorinated sulfonic acids (PFSAs) displayed comparable affinity, but no binding was detected for the two fluorotelomer alcohols. Circular dichroism results showed that PFC binding induced distinctive structural changes of the protein. Molecular docking revealed that the driving forces for the binding of PFCs with FABP were predominantly hydrophobic and hydrogen-bonding interactions, and the binding geometry was dependent on both the size and rigidity of the PFCs. Based on the binding constant obtained in this work, the possibility of in vivo competitive displacement of fatty acids from FABP by PFCs was estimated.	●	●	●							-		B	B
319	TK	Zhao, W.; Zitzow, J. D.; Weaver, Y.; Ehresman, D. J.; Chang, S. C.; Butenhoff, J. L.; Hagenbuch, B.	Isomer-Specific Transplacental Efficiencies of Perfluoroalkyl Substances in Human Whole Blood	2017	Toxicol Sci. 2017 Mar 1;156(1):84-95. doi: 10.1093/toxsci/kfw236.	Perfluoroalkyl sulfonates (PFSAs) such as perfluorohexane sulfonate (PFHxS) and perfluorooctane sulfonate (PFOS) have very long serum elimination half-lives in humans, and preferentially distribute to serum and liver. The enterohepatic circulation of PFHxS and PFOS likely contributes to their extended elimination half-lives. We previously demonstrated that perfluorobutane sulfonate (PFBS), PFHxS, and PFOS are transported into hepatocytes both in a sodium-dependent and a sodium-independent manner. We identified Na+/taurocholate cotransporting polypeptide (NTCP) as the responsible sodium-dependent transporter. Furthermore, we demonstrated that the human apical sodium-dependent bile salt transporter (ASBT) contributes to the intestinal reabsorption of PFOS. However, so far no sodium-independent uptake transporters for PFSAs have been identified in human hepatocytes or enterocytes. In addition, perfluoroalkyl carboxylates (PFCAs) with 8 and 9 carbons were shown to preferentially distribute to the liver of rodents; however, no rat or human liver uptake transporters are known to transport these PFCAs. Therefore, we tested whether PFBS, PFHxS, PFOS, and PFCAs with 44752 carbons are substrates of organic anion transporting polypeptides (OATPs). We used CHO and HEK293 cells to demonstrate that human OATP1B1, OATP1B3, and OATP2B1 can transport PFBS, PFHxS, PFOS, and the 2 PFCAs (C8 and C9). In addition, we show that rat OATP1A1, OATP1A5, OATP1B2, and OATP2B1 transport all 3 PFSAs. In conclusion, our results suggest that besides NTCP and ASBT, OATPs also are capable of contributing to the enterohepatic circulation and extended human serum elimination half-lives of the tested perfluoroalkyl acids.	●	●	●							-		A	B
320	TK	Zhao, W.; Zitzow, J. D.; Ehresman, D. J.; Chang, S. C.; Butenhoff, J. L.; Forster, J.; Hagenbuch, B.	Na+/taurocholate cotransporting polypeptide and apical sodium-dependent bile acid transporter are involved in the disposition of perfluoroalkyl sulfonates in humans and rats	2015	Toxicol Sci. 2015 Aug;146(2):363-73. doi: 10.1093/toxsci/kfv102. Epub 2015 May 21.	Among the perfluoroalkyl sulfonates (PFASs), perfluorohexane sulfonate (PFHxS), and perfluorooctane sulfonate (PFOS) have half-lives of several years in humans, mainly due to slow renal clearance and potential hepatic accumulation. Both compounds undergo enterohepatic circulation. To determine whether transporters involved in the enterohepatic circulation of bile acids are also involved in the disposition of PFASs, uptake of perfluorobutane sulfonate (PFBS), PFHxS, and PFOS was measured using freshly isolated human and rat hepatocytes in the absence or presence of sodium. The results demonstrated sodium-dependent uptake for all 3 PFASs. Given that the Na(+)/taurocholate cotransporting polypeptide (NTCP) and the apical sodium-dependent bile salt transporter (ASBT) are essential for the enterohepatic circulation of bile acids, transport of PFASs was investigated in stable CHO Flp-In cells for human NTCP or HEK293 cells transiently expressing rat NTCP, human ASBT, and rat ASBT. The results demonstrated that both human and rat NTCP can transport PFBS, PFHxS, and PFOS. Kinetics with human NTCP revealed Km values of 39.6, 112, and 130 μM for PFBS, PFHxS, and PFOS, respectively. For rat NTCP Km values were 76.2 and 294 μM for PFBS and PFHxS, respectively. Only PFOS was transported by human ASBT whereas rat ASBT did not transport any of the tested PFASs. Human OSTα/β was also able to transport all 3 PFASs. In conclusion, these results suggest that the long half-live and the hepatic accumulation of PFOS in humans are at least, in part, due to transport by NTCP and ASBT.	●	●	●							-		A	B
321	TK	Bischel, Heather N; Macmanus-Spencer, Laura A; Luthy, Richard G	Noncovalent interactions of long-chain perfluoroalkyl acids with serum albumin	2010	Environ Sci Technol. 2010 Jul 1;44(13):5263-9. doi: 10.1021/es101334s.	Preferential distribution of long-chain perfluoroalkyl acids (PFAAs) in the liver, kidney, and blood of organisms highlights the importance of PFAA-protein interactions in PFAA tissue distribution patterns. A serum protein association constant may be a useful parameter to characterize the bioaccumulative potential and in vivo bioavailability of PFAAs. In this work, association constants (K(a)) and binding stoichiometries for PFAA-albumin complexes are quantified over a wide range of PFAA:albumin mole ratios. Primary association constants for perfluorooctanoate (PFOA) or perfluorononanoate (PFNA) with the model protein bovine serum albumin (BSA) determined via equilibrium dialysis are on the order of 10(6) M(-1) with one to three primary binding sites. PFNA was greater than 99.9% bound to BSA or human serum albumin (HSA) at a physiological PFAA:albumin mole ratio (<10(-3)), corresponding to a high protein-water distribution coefficient (log K(PW) > 4). Nanoelectrospray ionization mass spectrometry (nanoESI-MS) data reveal PFAA-BSA complexes with up to eight occupied binding sites at a 4:1 PFAA:albumin mole ratio. Association constants estimated by nanoESI-MS are on the order of 10(5) M(-1) for PFOA and PFNA and 10(4) M(-1) for perfluorodecanoate and perfluorooctanesulfonate. The results reported here suggest binding through specific high affinity interactions at low PFAA:albumin mole ratios.			●							-		B	B
322	TK	Bischel, Heather N; Macmanus-Spencer, Laura A; Zhang, Chaojie; Luthy, Richard G	Strong associations of short-chain perfluoroalkyl acids with serum albumin and investigation of binding mechanisms	2011	Environ Toxicol Chem. 2011 Nov;30(11):2423-30. doi: 10.1002/etc.647. Epub 2011 Sep 14.	Interactions of perfluoroalkyl acids (PFAAs) with tissue and serum proteins likely contribute to their tissue distribution and bioaccumulation patterns. Protein-water distribution coefficients (K(PW)) based on ligand associations with bovine serum albumin (BSA) as a model protein were recently proposed as biologically relevant parameters to describe the environmental behavior of PFAAs, yet empirical data on such protein binding behavior are limited. In the present study, associations of perfluoroalkyl carboxylates (PFCAs) with two to 12 carbons (C_2-C_{12}) and perfluoroalkyl sulfonates with four to eight carbons (C_4, C_6, and C_8) with BSA are evaluated at low PFAA:albumin mole ratios and various solution conditions using equilibrium dialysis, nanoelectrospray ionization mass spectrometry, and fluorescence spectroscopy. Log K(PW) values for C_4 to C_{12} PFAAs range from 3.3 to 4.3. Affinity for BSA increases with PFAA hydrophobicity but decreases from the C_8 to C_{12} PFCAs, likely due to steric hindrances associated with longer and more rigid perfluoroalkyl chains. The C_4-sulfonate exhibits increased affinity relative to the equivalent chain-length PFCA. Fluorescence titrations support evidence that an observed dependence of PFAA-BSA binding on pH is attributable to conformational changes in the protein. Association constants determined for perfluorobutanesulfonate and perfluoropentanoate with BSA are on the order of those for long-chain PFAAs (K(a) ~10^6/M), suggesting that physiological implications of strong binding to albumin may be important for short-chain PFAAs.			●	●						-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
323	TK	Bogdanska, Jasna; Sundström, Maria; Bergström, Ulrika; Borg, Daniel; Abedi-Valugerdi, Manuchehr; Bergman, Åke; DePierre, Joseph; Nobel, Stefan	Tissue distribution of 35S-labelled perfluorobutanesulfonic acid in adult mice following dietary exposure for 1-5 days	2014	Chemosphere. 2014 Mar;98:28-36. doi: 10.1016/j.chemosphere.2013.09.062. Epub 2013 Nov 14.	Perfluorobutanesulfonyl fluoride (PBSF) has been introduced as a replacement for its eight-carbon homolog perfluorooctanesulfonyl fluoride (POSF) in the manufacturing of fluorochemicals. Fluorochemicals derived from PBSF may give rise to perfluorobutanesulfonic acid (PFBS) as a terminal degradation product. Although basic mammalian toxicokinetic data exist for PFBS, information on its tissue distribution has only been reported in one study focused on rat liver. Therefore, here we characterized the tissue distribution of PFBS in mice in the same manner as we earlier examined its eight-carbon homolog perfluorooctanesulfonate (PFOS) to allow direct comparisons. Following dietary exposure of adult male C57/BL6 mice for 1, 3 or 5d to 16 mg (35)S-PFBS kg(-1) d(-1), both scintillation counting and whole-body autoradiography (WBA) revealed the presence of PFBS in all of the 20 different tissues examined, demonstrating its ability to leave the bloodstream and enter tissues. After 5d of treatment the highest levels were detected in liver, gastrointestinal tract, blood, kidney, cartilage, whole bone, lungs and thyroid gland. WBA revealed relatively high levels of PFBS in male genital organs as well, with the exception of the testis. The tissue levels increased from 1 to 3 d of exposure but appeared thereafter to level-off in most cases. The estimated major body compartments were whole bone, liver, blood, skin and muscle. This exposure to PFBS resulted in 5-40-fold lower tissue levels than did similar exposure to PFOS, as well as in a different pattern of tissue distribution, including lower levels in liver and lungs relative to blood.			●	●						-		C	C
324	TK	Brantsæter, A L; Whitworth, K W; Ydersbond, T A; Haug, L S; Haugen, M; Knutsen, H K; Thomsen, C; Meltzer, H M; Becher, G; Sabaredzovic, A; Hoppin, J A; Eggesbø, M; Longnecker, M P	Determinants of plasma concentrations of perfluoroalkyl substances in pregnant Norwegian women	2013	Environ Int. 2013 Apr;54:74-84. doi: 10.1016/j.envint.2012.12.014. Epub 2013 Feb 15.	BACKGROUND: Perfluoroalkyl substances (PFASs) are widespread pollutants that have been associated with adverse health effects although not on a consistent basis. Diet has been considered the main source of exposure. The aim of the present study was to identify determinants of four plasma PFASs in pregnant Norwegian women. METHODS: This study is based in the Norwegian Mother and Child Cohort Study (MoBa) conducted by the Norwegian Institute of Public Health. Our sample included 487 women who enrolled in MoBa from 2003 to 2004. A questionnaire regarding sociodemographic, medical, and reproductive history was completed at 17 weeks of gestation and a dietary questionnaire was completed at 22 weeks of gestation. Maternal plasma samples were obtained around 17 weeks of gestation. Plasma concentrations of four PFASs (perfluorooctane sulfonate (PFOS), perfluorooctanoate (PFOA), perfluorohexane sulfonate (PFHxS), and perfluorononanoate (PFNA)) were examined in relation to demographic, lifestyle, dietary, and pregnancy-related covariates. Predictors were identified by optimizing multiple linear regression models using Akaike's information criterion (AIC). RESULTS: Parity was the determinant with the largest influence on plasma PFAS concentrations, with r(2) between 0.09 and 0.32 in simple regression models. In optimal multivariate models, when compared to nulliparous women, parous women had 46%, 70%, 19%, and 62% lower concentrations of PFOS, PFOA, PFHxS, and PFNA respectively (p<0.001 except for PFHxS, p<0.01). In all these models, duration of breastfeeding was associated with reduced PFAS levels. PFOA showed the largest reduction from breastfeeding, with a 2-3% reduction per month of breastfeeding in typical cases. Levels of PFOS, PFOA, and PFNA increased with time since most recent pregnancy. While pregnancy-related factors were the most important predictors, diet was a significant factor explaining up to 4% of the variance. One quartile increase in estimated dietary PFAS intake was associated with plasma PFOS, PFOA, PFHxS, and PFNA concentration increases of 7.2%, 3.3%, 5.8% and 9.8%, respectively, resulting in small, although non-trivial absolute changes in PFAS concentrations. CONCLUSION: Previous pregnancies and breastfeeding duration were the most important determinants of PFASs in this sample of pregnant women.			●	●						-		B	B
325	TK	Butenhoff, John L; Bjork, James A; Chang, Shu-Ching; Ehresman, David J; Parker, George A; Das, Kaberi; Lau, Christopher; Lieder, Paul H; van Otterdijk, François M; Wallace, Kendall B	Toxicological evaluation of ammonium perfluorobutyrate in rats: twenty-eight-day and ninety-day oral gavage studies	2012	Reprod Toxicol. 2012 Jul;33(4):513-530. doi: 10.1016/j.reprotox.2011.08.004. Epub 2011 Aug 19.	Sequential 28-day and 90-day oral toxicity studies were performed in male and female rats with ammonium perfluorobutyrate (NH(4)(+)PFBA) at doses up to 150 and 30mg/kg-d, respectively. Ammonium perfluorooctanoate was used as a comparator at a dose of 30mg/kg-d in the 28-day study. Female rats were unaffected by NH(4)(+)PFBA. Effects in males included: increased liver weight, slight to minimal hepatocellular hypertrophy; decreased serum total cholesterol; and reduced serum thyroxin with no change in serum thyrotropin. During recovery, liver weight, histological, and cholesterol effects were resolved. Results of RT-qPCR were consistent with increased transcriptional expression of the xenosensor nuclear receptors PPARα and CAR as well as the thyroid receptor, and decreased expression of Cyp1A1 (Ah receptor-regulated). No observable adverse effect levels (NOAELs) were 6 and >150mg/kg-d for male and female rats in the 28-day study and 6 and >30mg/kg-d in the 90-dat study, respectively.			●	●						-		C	C
326	TK	Chang, Shu-Ching; Thibodeaux, Julie R; Eastvold, Mary L; Ehresman, David J; Bjork, James A; Froehlich, John W; Lau, Christopher; Singh, Ravinder J; Wallace, Kendall B; Butenhoff, John L	Thyroid hormone status and pituitary function in adult rats given oral doses of perfluorooctanesulfonate (PFOS)	2008	Toxicology. 2008 Jan 20;243(3):330-9. doi: 10.1016/j.tox.2007.10.014. Epub 2007 Oct 26.	INTRODUCTION: Perfluorooctanesulfonate (PFOS) is widely distributed and persistent in humans and wildlife. Prior toxicological studies have reported decreased total and free thyroid hormones in serum without a major compensatory rise in thyrotropin (TSH) or altered thyroid gland histology. Although these animals (rats, mice and monkeys) might have maintained an euthyroid state, the basis for hypothyroxinemia remained unclear. We undertook this study to investigate the causes for the PFOS-induced reduction of serum total thyroxine (TT4) in rats. HYPOTHESES: We hypothesized that exposure to PFOS may increase free thyroxine (FT4) in the rat serum due to the ability of PFOS to compete with thyroxine for binding proteins. The increase in FT4 would increase the availability of the thyroid hormone to peripheral tissues for utilization, metabolic conversation, and excretion. We also hypothesized that PFOS does not directly interfere with the regulatory functions of the hypothalamic-pituitary-thyroid (HPT) axis in rats. EXPERIMENTS: Three experimental designs were employed to test these hypotheses. (1) Female Sprague-Dawley (SD) rats were given a single oral dose of 15 mg potassium PFOS/kg body weight. At intervals of 2, 6, and 24h thereafter, measurements were made for serum FT4, TT4, triiodothyronine (TT3), reverse triiodothyronine (rT3), thryrotropin (TSH), and PFOS concentrations, as well as liver PFOS concentrations, UDP-glucuronosyltransferase 1A (UGT1A) family mRNA transcripts, and malic enzyme (ME) mRNA transcripts and activity. (2) To provide evidence for increased uptake and metabolism of thyroxine (T4), 125 I-T4 was given to male and female SD rats by intravenous injection, followed in 2h by a single oral dose of 15 mg potassium PFOS/kg body weight. 125 I radioactivity was determined in urine and feces collected over a 24-h period and in serum and liver collected at 24h. (3) To assess the potentials effect of PFOS on the hypothalamic-pituitary-thyroid axis, over an 8-day period, groups of male SD rats were given PFOS (3mg/kg-d), propyl thiouracil (PTU, 10 microg/mL in water), or PTU and PFOS in combination, with controls receiving 0.5% Tween 20 vehicle. On days 1, 3, 7, and 8, TT4, TT3, and TSH were monitored. On day 8, pituitaries were removed and placed in static culture for assessment of thyrotropin releasing hormone (TRH)-mediated release of TSH. RESULTS: (1) PFOS transiently increased FT4 and decreased TSH within 6h, with values returning to control levels by 24h. TT4 was decreased by 55% over a 24-h period. TT3 and rT3 were decreased at 24h to a lesser extent than TT4. ME mRNA transcripts were increased at 2h and activity was increased at 24h. UGT1A mRNA transcripts were increased at 2 and 6h. (2) 125 I decreased in serum and liver relative to controls and consistent with a reduction in serum TT4. Concomitantly, 125 I activity was increased in urine and feces collected from PFOS-treated rats. (3) During the 8 days of dosing with PFOS, TSH was not elevated in male rats, while TT4 and TT3 were decreased. Pituitary response to TRH-mediated TSH release was not diminished after 8-daily oral doses of PFOS. CONCLUSIONS: These findings suggest that oral dosing in rats with PFOS results in transiently increased tissue availability of the thyroid hormones and turnover of T4 with a resulting reduction in serum TT4. PFOS does not induce a classical hypothyroid state under dosing conditions employed nor does it alter HPT activities.			●	●	●					-		-	B
327	TK	Dagnino, Sonia; Strynar, Mark J; McMahen, Rebecca L; Lau, Christopher S; Ball, Carol; Garantziotis, Stavros; Webster, Thomas F; McClean, Michael D; Lindstrom, Andrew B	Identification of biomarkers of exposure to FTOHs and PAPs in humans using a targeted and nontargeted analysis approach	2016	Environ Sci Technol. 2016 Sep 20;50(18):10216-25. doi: 10.1021/acs.est.6b01170. Epub 2016 Sep 12.	Although historic perfluorinated compounds are currently under scrutiny and growing regulatory control in the world, little is known about human exposure to other polyfluorinated compounds presently in use. Fluorotelomer alcohols (FTOHs) and polyfluoroalkyl phosphate esters (PAPs) are known to degrade to terminal perfluorinated acids and toxic reactive intermediates through metabolic pathways. Therefore, it is important to characterize their human exposure by the identification of unique biomarkers. With the use of liquid chromatography-mass spectrometry-time-of-flight analysis (LC-MS-TOF), we developed a workflow for the identification of metabolites for the 8:2 FTOH and 8:2 diPAP. Analysis of serum and urine of dosed rats indicated the 8:2 FTOH-sulfate and the 8:2 diPAP as potential biomarkers. These compounds, as well as 25 other fluorinated compounds and metabolites, were analyzed in human serum and urine samples from the general population (n = 100) and office workers (n = 30). The 8:2 FTOH-sulfate was measured for the first time in human samples in 5 to 10% of the serum samples, ranging from 50 to 80 pg/mL. The 8:2 diPAP was measured in 58% of the samples, ranging from 100 to 800 pg/mL. This study indicates the FTOH-sulfate conjugate as a biomarker of exposure to FTOHs and PAPs in humans.			●							-		A	B
328	TK	De Silva, Amila O; Benskin, Jonathan P; Martin, Leah J; Arsenault, Gilles; McCrindle, Robert; Riddell, Nicole; Martin, Jonathan W; Mabury, Scott A	Disposition of perfluorinated acid isomers in Sprague-Dawley rats; part 2: subchronic dose	2009	Environ Toxicol Chem. 2009 Mar;28(3):555-67. doi: 10.1897/08-254.1. Epub 2008 Oct 21.	Two major industrial synthetic pathways have been used to produce perfluorinated acids (PFAs) or their precursors: Telomerization and electrochemical fluorination (ECF). Products of telomer and ECF origin can be distinguished by structural isomer profiles. A mixture of linear and branched perfluoroalkyl isomers is associated with ECF. Telomer products characteristically consist of a single perfluoroalkyl geometry, typically linear. In biota, it is unclear if the isomer profile is conserved relative to the exposure medium and hence whether PFA isomer profiles in organisms are useful for distinguishing environmental PFA sources. A companion study suggested isomer-specific disposition following a single oral gavage exposure to rats. To confirm these findings under a more realistic subchronic feeding scenario, male and female rats were administered PFA isomers by diet for 12 weeks, followed by a 12-week depuration period. The diet contained 500 ng/g each of ECF perfluorooctanoate (PFOA, approximately 80% n-PFOA), ECF perfluorooctane sulfonate (PFOS, approximately 70% n-PFOS), and linear and isopropyl perfluorononanoate (n- and iso-PFNA). Blood sampling during the exposure phase revealed preferential accumulation of n-PFOA and n-PFNA compared to most branched isomers. Female rats depurated all isomers faster than males. Both sexes eliminated most branched perfluorocarboxylate isomers more rapidly than the n-isomer. Elimination rates of the major branched PFOS isomers were not statistically different from n-PFOS. Two minor isomers of ECF PFOA and one branched PFOS isomer had longer elimination half-lives than the n-isomers. Although extrapolation of these pharmacokinetics trends in rats to humans and wildlife requires careful consideration of dosage level and species-specific physiology, cumulative evidence suggests that perfluorocarboxylate isomer profiles in biota may not be suitable for quantifying the relative contributions of telomer and ECF sources.			●	●	●					-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献①ラン	文献②ラン
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
329	TK	D'eon, Jessica C; Mabury, Scott A	Exploring indirect sources of human exposure to perfluoroalkyl carboxylates (PFCAs): evaluating uptake, elimination, and biotransformation of polyfluoroalkyl phosphate esters (PAPs) in the rat	2011	Environ Health Perspect. 2011 Mar;119(3):344-50. doi: 10.1289/ehp.1002409. Epub 2010 Nov 8.	BACKGROUND: Perfluorinated carboxylic acids (PFCAs) are ubiquitous in human sera worldwide. Biotransformation of the polyfluoroalkyl phosphate esters (PAPs) is a possible source of PFCA exposure, because PAPs are used in food-contact paper packaging and have been observed in human sera. OBJECTIVES: We determined pharmacokinetic parameters for the PAP monoesters (monoPAPs) and PAP diesters (diPAPs), as well as biotransformation yields to the PFCAs, using a rat model. METHODS: The animals were dosed intravenously or by oral gavage with a mixture of 4:2, 6:2, 8:2, and 10:2 monoPAP or diPAP chain lengths. Concentrations of the PAPs and PFCAs, as well as metabolic intermediates and phase II metabolites, were monitored over time in blood, urine, and feces. RESULTS: The diPAPs were bioavailable, with bioavailability decreasing as the chain length increased from 4 to 10 perfluorinated carbons. The monoPAPs were not absorbed from the gut; however, we found evidence to suggest phosphate-ester cleavage within the gut contents. We observed biotransformation to the PFCAs for both monoPAP and diPAP congeners. CONCLUSIONS: Using experimentally derived biotransformation yields, perfluorooctanoic acid (PFOA) sera concentrations were predicted from the biotransformation of 8:2 diPAP at concentrations observed in human serum. Because of the long human serum half-life of PFOA, biotransformation of diPAP even with low-level exposure could over time result in significant exposure to PFOA. Although humans are exposed directly to PFCAs in food and dust, the pharmacokinetic parameters determined here suggest that PAP exposure should be considered a significant indirect source of human PFCA contamination.			●							-		B	B
330	TK	Fasano, William J; Carpenter, Stephen C; Gannon, Shawn A; Snow, Timothy A; Stadler, Judith C; Kennedy, Gerald L; Buck, Robert C; Korzeniowski, Stephen H; Hinderliter, Paul M; Kemper, Raymond A	Absorption, distribution, metabolism, and elimination of 8-2 fluorotelomer alcohol in the rat	2006	Toxicol Sci. 2006 Jun;91(2):341-55. doi: 10.1093/toxsci/kfj160. Epub 2006 Mar 16.	The absorption, distribution, metabolism, and elimination of [3-14C] 8-2 fluorotelomer alcohol (8-2 FTOH, C7F1514CF2CH2CH2OH) following a single oral dose at 5 and 125 mg/kg in male and female rats have been determined. Following oral dosing, the maximum concentration of 8-2 FTOH in plasma occurred by 1 h postdose and cleared rapidly with a half-life of less than 5 h. The internal dose to 8-2 FTOH, as measured by area under the concentration-time curve to infinity, was similar for male and female rats and was observed to increase in a dose-dependent fashion. The majority of the 14C 8-2 FTOH (> 70%) was excreted in feces, and 37-55% was identified as parent. Less than 4% of the administered dose was excreted in urine, which contained low concentrations of perfluorooctanoate (approximately 1% of total 14C). Metabolites identified in bile were principally composed of glucuronide and glutathione conjugates, and perfluorohexanoate was identified in excreta and plasma, demonstrating the metabolism of the parent FTOH by sequential removal of multiple CF2 groups. At 7 days postdose, 4-7% of the administered radioactivity was present in tissues, and for the majority, 14C concentrations were greater than whole blood with the highest concentration in fat, liver, thyroid, and adrenals. Distribution and excretion of a single 125-mg/kg [3-14C] 8-2 FTOH dermal dose following a 6-h exposure in rats was also determined. The majority of the dermal dose either volatilized from the skin (37%) or was removed by washing (29%). Following a 6-h dermal exposure and a 7-day collection period, excretion of total radioactivity via urine (< 0.1%) and feces (< 0.2%) was minor, and radioactivity concentrations in most tissues were below the limit of detection. Systemic availability of 8-2 FTOH following dermal exposure was negligible.			●	●						-		B	B
331	TK	Fasano, William J; Sweeney, Lisa M; Mawn, Michael P; Nabb, Diane L; Szostek, Bogdan; Buck, Robert C; Gargas, Michael L	Kinetics of 8-2 fluorotelomer alcohol and its metabolites, and liver glutathione status following daily oral dosing for 45 days in male and female rats	2009	Chem Biol Interact. 2009 Jul 15;180(2):281-95. doi: 10.1016/j.cbi.2009.03.015. Epub 2009 Mar 27.	Fluorotelomer alcohols (FTOHs) are raw materials used in the manufacture of polymeric and surfactant products. Based on previous findings from single oral dosing in rats with radiolabeled 8-2 FTOH, glutathione (GSH) depletion and/or the presence of perfluorinated/polyfluorinated acids and aldehyde metabolites was hypothesized to account for the hepatocellular lesions observed in male rats from a 90-day subchronic oral dosing study. Further, the reported nephropathy in female rats from the subchronic experiment was hypothesized to have been initiated by a thiol metabolite produced by degradation of GSH conjugates. In the current investigation, the kinetics of 8-2 FTOH and its metabolites along with liver GSH status were evaluated in the rat following daily oral dosing with 8-2 FTOH for 45 days at 5 and 125 mg/kg/day. Liver GSH stores 1-2h after dosing were unaffected, suggesting that GSH depletion is not likely a relevant mode of action in the liver. The tissue metabolite data indicate that the liver toxicity mode of action is likely associated with elevated levels of perfluoroalkyl acids found in males, since other polyfluorinated metabolites and 8-2 FTOH were present in livers from female rats at comparable or higher levels. Detection of the N-acetyl cysteine conjugate of the unsaturated parent telomer alcohol in urine from female rats and not male rats provides some evidence to support the mechanistic basis for the observed kidney effects. Further, the increasing levels of perfluorooctanoic acid (PFOA) in plasma from female rats over the 45-day dosing phase, while unexpected, may reflect an increased net absorption of 8-2 FTOH, slow elimination of intermediates in the metabolic pathway between 8-2 FTOH and PFOA, or altered kidney clearance. The results of this study have enhanced our understanding of 8-2 FTOH kinetics and metabolism and potential modes of action in the rat, which will guide the design of future studies for FTOHs and our need to define the mechanistic basis for the observed effects.			●							-		B	B
332	TK	Fisher, Mandy; Arbuckle, Tye E; Liang, Chun Lei; LeBlanc, Alain; Gaudreau, Eric; Foster, Warren G; Haines, Douglas; Davis, Karelyn; Fraser, William D	Concentrations of persistent organic pollutants in maternal and cord blood from the maternal-infant research on environmental chemicals (MIREC) cohort study	2016	Environ Health. 2016 May 4;15(1):59. doi: 10.1186/s12940-016-0143-y.	BACKGROUND: Pregnant women are an especially important population to monitor for environmental exposures given the vulnerability of the developing fetus. During pregnancy and lactation chemical body burdens may change due to the significant physiological changes that occur. Developmental exposures to some persistent organic pollutants (POPs) have been linked with adverse health outcomes. METHODS: First trimester maternal and cord blood plasma concentrations of several POPs including polychlorinated biphenyls (PCBs), organochlorine pesticides (OCs), polybrominated diphenyl ethers (PBDE)s and perfluoroalkyl substances (PFASs) were measured in samples from 1983 pregnant women enrolled in the Maternal-Infant Research on Environmental Chemicals (MIREC) cohort. Predictors of exposure were also identified. RESULTS: In maternal plasma, there was >90 % detection for the perfluoroalkyl substances (PFASs) perfluorooctanoic acid (PFOA), perfluoroctane sulfonate (PFOS), perfluorohexane sulfonate (PFHxS), and dichlorodiphenyldichloroethylene (DDE), oxychlordane and PCB 138 and 153. Cord blood plasma had much lower detection rates with low or very limited detection for most PCBs and PBDEs. The PFASs were the most frequently detected (23-64 %) chemical class in cord plasma. In a subset of 1st and 3rd trimester paired samples, PFAS concentrations were found to be strongly correlated and had ICCs ranging from 0.64 (PFOA) to 0.83 (PFHxS). The cord:maternal plasma concentration ratios ranged from 0.14 (PFOS) to 0.87 (oxychlordane, lipid adjusted). Similar to o pre-pregnancy BMI and fish consumption to be significant predictors for most chemicals. Those participants who were foreign-born had significantly higher concentrations of organochlorinated pesticides and PCBs. CONCLUSIONS: In the MIREC study, multiple chemical contaminants were quantified in the plasma of pregnant women. In cord plasma PFOA had the highest detection rate. However, compared to other Canadian and international population studies, the MIREC participants had lower contaminant concentrations of these substances.ther studies, we found parity, maternal age, income, education, smoking status,			●	●						-		B	B
333	TK	Gaillard, Juliette; Veyrand, Bruno; Thomas, Marielle; Dauchy, Xavier; Boiteux, Virginie; Marchand, Philippe; Le Bizec, Bruno; Banas, Damien; Feidt, Cyril	Tissue uptake, distribution, and elimination of perfluoroalkyl substances in juvenile perch through perfluorooctane sulfonamidoethanol based phosphate diester dietary exposure	2017	Environ Sci Technol. 2017 Jul 5;51(13):7658-7666. doi: 10.1021/acs.est.6b05598. Epub 2017 Jun 22.	Perfluorooctane sulfonamidoethanol based phosphate diester (SAmPAP) is a potential perfluorooctanesulfonate (PFOS) precursor. To examine whether SAmPAP exposure would result in fish contamination by perfluoroalkyl and polyfluoroalkyl substances (PFASs), juvenile Eurasian perch were dietarily exposed to this compound (dosed group) or exposed to the same tank water but fed control feed (control group). SAmPAP and metabolites were monitored in the muscle, liver, and serum during the 45-day exposure phase and 35-day depuration phase. SAmPAP was only detected in the dosed group and the absorption efficiency (0.04-2.25%) was very low, possibly related to its low bioavailability in the gastrointestinal tract, steric constraints in crossing biological membranes, and clearing by enterohepatic circulation. Although SAmPAP was biotransformed and eliminated at a slow rate (t(1/2) > 18 days), its biomagnification factor was low. The observed metabolites in fish were N-ethyl perfluorooctane sulfonamidoacetic acid, perfluorooctane sulfonamidoacetic acid, perfluorooctane sulfonamide, and PFOS. Considering that SAmPAP was the only source of PFASs in the tanks, the occurrence of metabolites indicates that SAmPAP could be biotransformed in fish and contribute to PFOS bioaccumulation. However, levels of metabolites were not significantly different in the dosed and control groups, indicating that metabolite excretion followed by re-exposure to these metabolites from water was the main uptake route.			●							-		B	B
334	TK	Gannon, Shawn A; Johnson, Terry; Nabb, Diane L; Serex, Tessa L; Buck, Robert C; Loveless, Scott E	Absorption, distribution, metabolism, and excretion of [1-14C]-perfluorohexanoate ([14C]-PFHx) in rats and mice	2011	Toxicology. 2011 Apr 28;283(1):55-62. doi: 10.1016/j.tox.2011.02.004. Epub 2011 Feb 22.	The absorption, tissue distribution, elimination, and metabolism of [1-^{14}C]-PFHx in rats and mice dosed orally at 2 or 100 mg/kg was evaluated following a single dose or after 14 consecutive doses. Absorption was rapid in rats as evidenced by a short time to maximum concentration (C(max)) of 30 min in male rats and 15 min in female rats at both the 2 and 100mg/kg dose level. The plasma elimination half-life was somewhat longer in males (1.5-1.7 h) than in females (0.5-0.7 h). Absorption in the mouse was also rapid with the maximum plasma concentration occurring between 15 and 30 min after dosing. The maximum concentration was not appreciably different between male and female mice (8 µg equiv./g at 2 mg/kg; ~350 µg equiv./g at 100 mg/kg). The primary route of elimination was via the urine. PFHx was not metabolized in rat or mouse hepatocytes, nor were any metabolites observed after oral dosing in either rodent species. Essentially 100% of the dose was eliminated in urine within 24 h demonstrating that PFHx is readily absorbed and bioavailability approaches 100%, even at a dose as high as 100 mg/kg. The route and extent of elimination was unchanged after 14 days of daily dosing. Tissues were collected at three time points (rat: 0.5, 2, and 24 h; mice: 0.25, 1, and 24 h) after dosing to investigate the tissue clearance kinetics of PFHx following a single dose at 2 or 100 mg/kg. In all tissues except skin, PFHx was not quantifiable 24 h after dosing in both sexes of the two species.			●	●						-		A	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献①ラン	文献②ラン
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
335	TK	Gomis, Melissa I; Vestergren, Robin; Borg, Daniel; Cousins, Ian T	Comparing the toxic potency in vivo of long-chain perfluoroalkyl acids and fluorinated alternatives	2018	Environ Int. 2018 Apr;113:1-9. doi: 10.1016/j.envint.2018.01.011. Epub 2018 Jan 28.	Since 2000, long-chain perfluoroalkyl acids (PFAAs) and their respective precursors have been replaced by numerous fluorinated alternatives. The main rationale for this industrial transition was that these alternatives were considered less bioaccumulative and toxic than their predecessors. In this study, we evaluated to what extent differences in toxicological effect thresholds for PFAAs and fluorinated alternatives, expressed as administered dose, were confounded by differences in their distribution and elimination kinetics. A dynamic one-compartment toxicokinetic (TK) model for male rats was constructed and evaluated using test data from toxicity studies for perfluorobutanoic acid (PFBA), perfluorohexanoic acid (PFHxA), perfluorobutane sulfonic acid (PFBS), perfluorooctanoic acid (PFOA), perfluorooctanesulfonic acid (PFOS) and ammonium 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)-propanoate (GenX). Dose-response curves of liver enlargement from sub-chronic oral toxicity studies in male rats were converted to internal dose in serum and in liver to examine the toxicity ranking of PFAAs and fluorinated alternatives. Converting administered doses into equivalent serum and liver concentrations reduced the variability in the dose-response curves for PFBA, PFHxA, PFOA and GenX. The toxicity ranking using modeled serum (GenX > PFOA > PFHxA > PFBA) and liver (GenX > PFOA ≈ PFHxA ≈ PFBA) concentrations indicated that some fluorinated alternatives have similar or higher toxic potency than their predecessors when correcting for differences in toxicokinetics. For PFOS and perfluorobutane sulfonic acid (PFBS) the conversion from administered dose to serum concentration equivalents did not change the toxicity ranking. In conclusion, hazard assessment based on internal exposure allows evaluation of toxic potency and bioaccumulation potential independent of kinetics and should be considered when comparing fluorinated alternatives with their predecessors.			●							-		-	B
336	TK	Guruge, Keerthi S; Noguchi, Michiko; Yoshioka, Koji; Yamazaki, Eriko; Taniyasu, Sachi; Yoshioka, Miyako; Yamanaka, Noriko; Ikezawa, Mitsutaka; Tanimura, Nobuhiko; Sato, Masumi; Yamashita, Nobuyoshi; Kawaguchi, Hiroaki	Microminipigs as a new experimental animal model for toxicological studies: comparative pharmacokinetics of perfluoroalkyl acids	2016	J Appl Toxicol. 2016 Jan;36(1):68-75. doi: 10.1002/jat.3145. Epub 2015 Apr 15.	In this study, we evaluated the efficacy of a novel minipig strain, the Microminipig (MMPig), as an animal model for studying the pharmacokinetics of a mixture of 10 perfluoroalkyl acids (PFAAs). After a single oral dose was given, we found that the blood depuration of PFAAs (blood t1/2), which we calculated using first-order elimination curves, ranged from 1.6 to 86.6 days. Among the five body compartments analyzed, the liver was the greatest site of accumulation of perfluorooctanesulfonate and longer chain perfluorinated carboxylates such as perfluorodecanoic acid, perfluoroundecanoic acid and perfluorododecanoic acid. We observed an increasing accumulation trend of perfluorinated carboxylates in the organs associated with the fluorinated carbon chain length. The perfluorononanoic acid burden was the highest among the treated compounds 21 days after a single exposure, as 29% of the given perfluorononanoic acid dose was accumulated in the tissues. The persistence of PFAAs in edible pig tissues even after 21 days post-exposure raises concerns about the safety of swine products. This was the first study to use MMPigs to elucidate the pharmacokinetics of a group of environmental pollutants. We found that MMPigs could be excellent experimental animals for toxicological studies due to their easy handling, cost efficacy for target compounds and ease of waste treatment.			●							-		B	D
337	TK	Hagen, D F; Belisle, J; Johnson, J D; Venkateswarlu, P	Characterization of fluorinated metabolites by a gas chromatographic-helium microwave plasma detector	1981	Anal Biochem. 1981 Dec;118(2):336-43. doi: 10.1016/0003-2697(81)90591-1.	No abstract available			●							-		B	D
338	TK	Han, Xing; Nabb, Diane L; Russell, Mark H; Kennedy, Gerald L; Rickard, Robert W	Renal elimination of perfluorocarboxylates (PFCAs)	2012	Chem Res Toxicol. 2012 Jan 13;25(1):35-46. doi: 10.1021/tx200363w. Epub 2011 Oct 25.	Sex-, species-, and chain length-dependent renal elimination is the hallmark of mammalian elimination of perfluorocarboxylates (PFCAs) and has been extensively studied for almost 30 years. In this review, toxicokinetic data of PFCAs (chain lengths ranging from 4 to 10) in different species are compared with an emphasis on their relevance to renal elimination. PFCAs vary in their affinities to bind to serum albumins in plasma, which is an important factor in determining the renal clearance of PFCAs. PFCA-albumin binding has been well characterized and is summarized in this review. The mechanism of the sex-, species-, and chain length-dependent renal PFCA elimination is a research area that has gained continuous interest since the beginning of toxicological studies of PFCAs. It is now recognized that organic anion transport proteins play a key role in PFCA renal tubular reabsorption, a process that is sex-, species-, and chain length-dependent. Recent studies on the identification of PFCA renal transport proteins and characterization of their transport kinetics have greatly improved our understanding of the PFCA renal transport mechanism at the molecular level. A mathematical representation of this renal tubular reabsorption mechanism has been incorporated in physiologically based pharmacokinetic (PBPK) modeling of perfluorooctanoate (PFOA). Improvement of PBPK models in the future will require more accurate and quantitative characterization of renal transport pathways of PFCAs. To that end, a basolateral membrane efflux pathway for the reabsorption of PFCAs in the kidney is discussed in this review, which could provide a future research direction toward a better understanding of the mechanisms of PFCA renal elimination.			●			●				-		B	B
339	TK	Hebert, Paul C; MacManus-Spencer, Laura A	Development of a fluorescence model for the binding of medium- to long-chain perfluoroalkyl acids to human serum albumin through a mechanistic evaluation of spectroscopic evidence	2010	Anal Chem. 2010 Aug 1;82(15):6463-71. doi: 10.1021/ac100721e.	A novel model for measuring the strength of perfluoroalkyl acid (PFAA) binding to human serum albumin (HSA) by use of the protein's native fluorescence is described. The model is derived from published properties of HSA and its interactions with other surfactants; it is consistent with these properties and experimental observations. The model's validity has been tested with both medium- to long-chain PFAAs (perfluoroheptanoate, perfluorooctanoate, perfluorononanoate, perfluorodecanoate, perfluoroundecanoate, perfluorohexanesulfonate, and perfluorooctanesulfonate) and short-chain PFAAs (perfluorohexanoate and perfluorobutanesulfonate). These experiments confirm the model as a valid description for the binding of medium- to long-chain PFAAs to HSA. Results indicate at least 2-3 PFAAs bind to each protein with affinity on the order of 10(4) M(-1). These binding strengths exhibit a dependence on protein concentration. Measured PFAA binding constants are approximately 10% of those values reported for fatty acids of similar chain length; correcting for protein concentration suggests the binding strengths may be as low as 2-3% of the corresponding fatty acids' affinities. Like fatty acids, the carboxylate PFAAs exhibit a trend of generally increasing binding strength with increased chain length. The model does not appear valid for the binding of short-chain PFAAs to HSA. Hill binding coefficients, fluorescence intensity measurements, and wavelengths of maximum emission suggest short-chain PFAAs associate with HSA differently and fail to promote the same conformational changes in the protein's tertiary structure as the medium- to long-chain PFAAs.			●							-		B	B
340	TK	Huang M.C.; Robinson, V G; Waidyanatha, S; Dzierlenga, A L; DeVito, M J; Eifrid, M A; Gibbs, S T; Blystone, C R	Toxicokinetics of 8:2 fluorotelomer alcohol (8:2-FTOH) in male and female Hsd: Sprague Dawley SD rats after intravenous and gavage administration	2019	Toxicol Rep. 2019 Aug 20;6:924-932. doi: 10.1016/j.toxrep.2019.08.009. eCollection 2019.	Fluorotelomer alcohols (FTOHs) are used in the production of persistent per- and polyfluorinated alkyl substances (PFAS). Rodents and humans metabolize FTOHs to perfluoralkyl carboxylic acids which have several associated toxicities. Thus, understanding the toxicokinetics of these FTOHs and their metabolites will be useful for interpreting their toxicity for humans. Here, male and female Hsd:Sprague-Dawley SD rats were administered a single dose of 8:2-FTOH via gavage (males: 12, 24, 48 mg/kg; females: 40, 80, 160 mg/kg) or IV (males: 12 mg/kg; females: 40 mg/kg). Toxicokinetics of 8:2-FTOH and two primary metabolites, perfluorooctanoic acid (PFOA) and 7:3-fluorotelomer acid (7:3-FTA) were determined in plasma. Concentrations (total) of these chemicals were determined in the liver, kidney, and brain. There was rapid absorption and distribution of 8:2-FTOH after gavage administration in male rats. The plasma elimination half-life ranged from 1.1 to 1.7 hours. Kinetic parameters of 8:2-FTOH in females were similar to that in males. Bioavailability of 8:2-FTOH ranged from 22 to 41% for both sexes with no dose-dependent trends. 8:2-FTOH metabolites, PFOA and 7:3-FTA were detected in plasma following administration of the parent FTOH. Consistent with existing literature, the plasma half-life of PFOA was longer in males than in females (198-353 hours and 4.47-6.9 hours, respectively). The plasma half-life of 7:3-FTA was around 2-3 days in both sexes. 8:2-FTOH and 7:3-FTA were detected in all tissues; PFOA was found in the liver and kidney but not the brain. Detectable concentrations of metabolites persisted longer than the parent FTOH. These data demonstrate that in rats given a single gavage dose, 8:2-FTOH is rapidly absorbed, metabolized to form PFOA and 7:3-FTA, distributed to tissues, and eliminated faster than its metabolites. Sex differences were observed in the tissue distribution and elimination of PFOA, but not 8:2-FTOH and 7:3-FTA.			●							-		A	B
341	TK	Iwai, Hiroyuki	Toxicokinetics of ammonium perfluorohexanoate	2011	Drug Chem Toxicol. 2011 Oct;34(4):341-6. doi: 10.3109/01480545.2011.585162. Epub 2011 Jun 22.	Excretion patterns and rates of ammonium perfluorohexanoate (APFHx) after administration of a single and multiple (14 days) oral dose(s) at 50 mg/kg to male and female mice and rats were examined. The test substance was [(14)C]-labeled APFHx. After a single oral administration, total excretion was rapid, with mean recoveries of over 90% of the dose at 24 hours after administration, irrespective of gender or species. The major route of elimination was via the urine (means of percentage recovery between 73.0 and 90.2% of the dose), followed by the feces (means of percentage recovery between 7.0 and 15.5% of the dose). Elimination via expired air was negligible. For the multiple dose tests, multiple (13 daily doses) oral administration of APFHx was followed by a single oral administration of [(14)C]-APFHx. Excretion was rapid, with mean recoveries of over 90% of the administered dose (mean values >95% of the ultimately recovered material) at 24 hours after dosing, irrespective of gender or species. The major route of elimination was via the urine (means of percentage recovery between 77.8 and 83.4% of the dose), followed by the feces (means of percentage recovery between 9.6 and 12.9% of the dose).			●	●						-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ラン①抽出	文献ラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
342	TK	Kim, Sook-Jin; Shin, Hwajin; Lee, Yong-Bok; Cho, Hea-Young	Sex-specific risk assessment of PFHxS using a physiologically based pharmacokinetic model	2018	Arch Toxicol. 2018 Mar;92(3):1113-1131. doi: 10.1007/s00204-017-2116-5. Epub 2017 Nov 16.	Perfluorohexanesulfonate (PFHxS), which belongs to the group of perfluoroalkyl and polyfluoroalkyl substances (PFASs), has been extensively used in industry and subsequently detected in the environment. Its use may be problematic, as PFHxS is known to induce neuronal cell death, and has been associated with early onset menopause in women and with attention deficit/hyperactivity disorder. Due to these impending issues, the aim of this study is to develop and evaluate a physiologically based pharmacokinetic (PBPK) model for PFHxS in male and female rats, and apply this to a human health risk assessment. We conducted this study in vivo after the oral or intravenous administration of PFHxS in male (dose of 10 mg/kg) and female rats (dose of 0.5-10 mg/kg). The biological samples consisted of plasma, nine tissues, urine, and feces. We analyzed the sample using ultra-liquid chromatography coupled tandem mass spectrometry (UPLC-MS/MS). Our findings showed the tissue-plasma partition coefficients for PFHxS were highest in the liver. The predicted rat plasma and tissue concentrations using a simulation fitted well with the observed values. We extrapolated the PBPK model in male and female rats to a human PBPK model of PFHxS based on human physiological parameters. The reference doses of 0.711 μg/kg/day (male) and 0.159 μg/kg/day (female) and external doses of 0.007 μg/kg/day (male) and 0.006 μg/kg/day (female) for human risk assessment were estimated using Korean biomonitoring values. This study provides valuable insight into human health risk assessment regarding PFHxS exposure.			●	●						-		B	B
343	TK	Hethey, Christoph; Mielke, Hans; Gundert-Remy, Ursula	Exploring sex differences in human health risk assessment for PFNA and PFDA using a PBPK model	2019	Arch Toxicol. 2019 Jun;93(6):1769-1770. doi: 10.1007/s00204-019-02480-z. Epub 2019 May 29.	No abstract available			●						-		C	D
344	TK	Kudo, N; Suzuki, E; Katakura, M; Ohmori, K; Noshiro, R; Kawashima, Y	Comparison of the elimination between perfluorinated fatty acids with different carbon chain length in rats	2001	Chem Biol Interact. 2001 Apr 16;134(2):203-16. doi: 10.1016/s0009-2797(01)00155-7.	Elimination in urine and feces was compared between four perfluorinated fatty acids (PFCAs) with different carbon chain length. In male rats, perfluoroheptanoic acid (PFHA) was rapidly eliminated in urine with the proportion of 92% of the dose being eliminated within 120 h after an intraperitoneal injection. Perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA) and perfluorodecanoic acid (PFDA) was eliminated in urine with the proportions of 55, 2.0 and 0.2% of the dose, respectively. By contrast, four PFCAs were eliminated in feces with the proportion of less than 5% of the dose within 120 h after an injection. In female rats, the proportions of PFOA and PFNA eliminated in urine within 120 h were 80% and 51% of the dose, respectively, which were significantly higher compared with those in male rats. There was the tendency that PFCA with longer carbon chain length is less eliminated in urine in both male and female rats. Fecal elimination of PFCAs was not different between PFCAs in female rats and comparable to those in male rats. The rates of biliary excretion of PFCAs in male rats were slower than those in female rats. Sex-related difference in urinary elimination of PFOA was abolished when male rats had been castrated. On the contrary, treatment with testosterone suppressed the elimination of PFOA in urine in both castrated male rats and female rats. The effect of testosterone was in a time- and dose-dependent manner. These results suggest that PFCAs are distinguished by their carbon chain length by a renal excretion system, which is regulated by testosterone.			●	●		●				-		B	B
345	TK	Kudo, Naomi; Iwase, Yuko; Okayachi, Hiroshi; Yamakawa, Yoshihiro; Kawashima, Yoichi	Induction of hepatic peroxisome proliferation by 8-2 telomer alcohol feeding in mice: formation of perfluorooctanoic acid in the liver	2005	Toxicol Sci. 2005 Aug;86(2):231-8. doi: 10.1093/toxsci/kfi191. Epub 2005 May 11.	The effects of dietary administration of 1H, 1H, 2H, 2H-perfluorodecanol (8-2 telomer alcohol), on peroxisome proliferation in the liver of mice were studied. Male ddY mice were fed on a diet containing 8-2 telomer alcohol at concentrations of 0, 0.025, 0.05, 0.1, and 0.2% (w/w) for 7, 14, 21, and 28 days. These treatments with 8-2 telomer alcohol caused liver enlargement in a dose- and duration-dependent manner. Peroxisome proliferation in the liver of mice was confirmed by electron microscopic examination. Peroxisomal acyl-CoA oxidase was induced by these treatments with 8-2 telomer alcohol in a dose- and time-dependent manner. The concentration of perfluorooctanoic acid (PFOA) and related compounds were determined in the liver and plasma, since PFOA had been shown to be a possible metabolite of 8-2 telomer alcohol and to cause significant peroxisome proliferation in rodents. Five metabolites, namely, perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), 2H, 2H-perfluorodecanoic acid (8-2 telomer acid), and two unidentified metabolites, were present in the liver and serum. PFOA was confirmed to be accumulated in the liver of mice following the administration of 8-2 telomer alcohol in a dose- and duration-dependent manner. A linear relationship was observed between the concentration of PFOA and the activity of peroxisomal acyl-CoA oxidase in the liver of mice. These results strongly suggest that PFOA, but not 8-2 telomer alcohol itself, caused peroxisome proliferation in the liver. The present study provided evidence that 8-2 telomer alcohol is converted into PFOA in vivo and that the PFOA formed produces biological effects in the liver of mice.			●	●						-		B	B
346	TK	Liu X, Fang M, Xu F and Chen D	Characterization of the binding of per- and poly-fluorinated	2019	Trends in Analytical Chemistry, 116, 177–185. doi: 10.1016/j.trac.2019.05.017	No abstract available			●						-		B	D
347	TK	Martin, Jonathan W; Mabury, Scott A; O'Brien, Peter J	Metabolic products and pathways of fluorotelomer alcohols in isolated rat hepatocytes	2005	Chem Biol Interact. 2005 Aug 15;155(3):165-80. doi: 10.1016/j.cbi.2005.06.007.	Fluorotelomer alcohols (FTOHs; CF(3)(CF(2))(x)C(2)H(4)OH; where x=3, 5, 7, 9) are a novel class of polyfluorinated contaminants, recently detected in the North American atmosphere, that are possible precursors to the series of perfluoroalkyl carboxylates (PFCAs) in human blood. An in vivo rat study validated earlier independent work that poly- and per-fluoroalkyl carboxylates were metabolites of FTOHs, but our detection of several novel metabolites prompted us to examine their pathways in greater detail using isolated rat hepatocytes. Using 8:2 FTOH (i.e. where x=7) as a model compound, the metabolic products formed by isolated rat hepatocytes were identified, and three synthesized intermediates were incubated separately to elucidate the metabolic pathways. For 8:2 FTOH, a major fate was direct conjugation to form the O-glucuronide and O-sulfate. Using 2,4-dinitrophenylhydrazine (DNPH) trapping, the immediate oxidation product of 8:2 FTOH was identified as 8:2 fluorotelomer aldehyde (8:2 FTAL; CF(3)(CF(2))(7)CH(2)C(H)O). 8:2 FTAL was transient and eliminated HF non-enzymatically to yield 8:2 fluorotelomer alpha,beta-unsaturated aldehyde (8:2 FTUAL; CF(3)(CF(2))(6)CFCHC(H)O) which was also short-liived and reacted GSH and perhaps other endogenous nucleophiles. Four polyfluorinated acid intermediates were also detected, including 8:2 fluorotelomer carboxylate (8:2 FTCA; CF(3)(CF(2))(7)CH(2)C(O)O(-)), 8:2 fluorotelomer alpha,beta-unsaturated carboxylate (8:2 FTUCA; CF(3)(CF(2))(6)CFCHC(O)O(-)), tetrahydroperfluorodecanoate (CF(3)(CF(2))(6)(CH(2))(2)CO(2)(-)), and dihydroperfluorodecenoate (CF(3)(CF(2))(6)CHCHCO(2)(-)). The pathways leading to 8:2 FTCA and FTUCA involve oxidation of 8:2 FTAL, however, the pathways leading to the latter two polyfluorinated acids remain inconclusive. The fate of the unsaturated metabolites, 8:2 FTUAL and FTUCA, included conjugation with GSH and dehydrofluorination to yield alpha,beta-unsaturated GSH conjugates, and GS-8:2 FTUAL which was subsequently reduced to the corresponding alcohol. Perfluorooctanoate (PFOA) and minor amounts of perfluorononanoate (PFNA) were confirmed as metabolites of 8:2 FTOH, and the respective roles of beta- and alpha-oxidation mechanisms are discussed. The analogous acids, aldehydes, and conjugated metabolites of 4:2, 6:2, and 10:2 FTOH (i.e. where x=3, 5, and 9, respectively) were also detected, and metabolite profiles among FTOHs generally differed only in the length of their perfluoroalkyl chains. Preincubation with aminobenzotriazole, but not pyrazole, inhibited the formation of metabolites from all FTOHs, suggesting that their oxidation was catalyzed by P450, not alcohol dehydrogenase.			●							-		B	B
348	TK	Nilsson, Helena; Kärrman, Anna; Rotander, Anna; van Bavel, Bert; Lindström, Gunilla; Westberg, Håkan	Professional ski waxers € ' exposure to PFAS and aerosol concentrations in gas phase and different particle size fractions	2013	Environ Sci Process Impacts. 2013 Apr;15(4):814-22. doi: 10.1039/c3em30739e.	Previous reports show that professional ski waxers have elevated blood levels of perfluorinated substances (PFAS) such as perfluorooctanoate (PFOA) and are exposed to very high concentrations of PFAS in air during ski waxing. Aerosol exposure increases the risk of cardiovascular disease, and PFOA is a potential hormonal disruptor and carcinogen, and can affect the fatty acid metabolism. Animal studies have shown that 8:2 FTOH can undergo biotransformation to PFOA. For the first time, this study presents an occupational scenario of professional ski waxers who are exposed to extremely high dust levels as well as per- and polyfluorinated compounds. Personal and fixed measurements of total aerosol, inhalable and respirable fractions were performed during World Cup events 2007-2010. The occupational exposure limit (OEL) is exceeded in 37% of the personal measurements with concentrations up to 15 mg m(-3) in air. There are differences between personal and area total aerosol concentrations with levels from personal measurements twice as high as those from the area measurements. The personal levels for FTOH ranged up to 996 μg m(-3) (mean = 114 μg m(-3)) and for PFOA up to 4.89 μg m(-3) (mean = 0.53 μg m(-3)) in ENV+ sorbent samples as compared to the general exposure levels from air reaching only low ng m(-3) (<30 ng m(-3)) levels. FTOHs were not detected in aerosols but PFOA showed an average level of 12 μg m(-3) (range = 1.2-47 μg m(-3)). The ski waxers' exposure to paraffin fumes and PFAS is not in compliance with the occupational exposure standards and by far exceed the general populations' exposure. Preventive measures must be taken to minimize the exposure in this occupational group.			●							-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報抽出対象	文献ランク①	文献ランク②
349	TK	Olsen, Geary W; Butenhoff, John L; Zobel, Larry R	Perfluoroalkyl chemicals and human fetal development: an epidemiologic review with clinical and toxicological perspectives	2009	Reprod Toxicol. 2009 Jun;27(3-4):212-230. doi: 10.1016/j.reprotox.2009.02.001. Epub 2009 Feb 20.	Epidemiologists began to focus on human developmental outcomes with perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) as a consequence of dose-dependent developmental toxicological studies that reported effects of lowered birth weight, increased postnatal mortality, and decreased postnatal growth in surviving rats and mice. Contributing to the epidemiologic interest was the widespread presence of PFOS and PFOA in the general population, lengthy serum elimination half-lives in humans, and the placental transfer of PFOS and PFOA in humans that was established via measurement of paired maternal and umbilical cord blood samples. The purpose of this paper is to qualitatively review the published epidemiologic literature as it pertains to the potential association of exposure to PFOS and PFOA with human fetal development. The published research has focused on birth weight and other measurements that reflect human fetal development. A total of eight epidemiologic studies were reviewed that focused on six general (non-occupational) and two occupational populations. Of the six general population studies, five examined associations between birth weight and other anthropometric measurements in relation to maternal blood and/or umbilical cord concentrations of PFOS and PFOA. In the sixth study, three geographical areas in Washington County, Ohio, were categorized by their public drinking water sources that contained PFOA that had resulted in higher serum concentrations than observed in other general population studies. The occupational studies focused on a perfluorochemical manufacturing site (Decatur, AL) with exposure categorized from work history and biomonitoring data. There were inconsistent associations reported for several different birth outcomes, including birth weight, birth length, head circumference, and ponderal index, among the five general population studies that measured PFOS and PFOA in the study subjects. No association with birth weight or gestational age was reported in the community drinking water study. Only one general population study examined infant Apgar scores and developmental milestones at 6 and 18 months of age with no associations reported. No association with self-reported birth weight and occupational exposure to PFOS materials was observed among female perfluorochemical production workers. These epidemiologic data are discussed in relation to their methodological strengths and weaknesses, coherence with toxicological results, consistency of associations between studies, and plausible alternative explanations. Epidemiological, clinical, and toxicological insights are offered that may be useful for human health risk characterization. Studies scheduled for completion in the next few years are also cited. An appendix to this review describes the results of the only investigation that attempted to determine whether a causal association existed between maternal (4-14 weeks gestation) PFOS and PFOA concentrations in a general population and fecundity, as measured by time to pregnancy (TTP). Important issues are addressed regarding the methods and data analysis that may limit inferences from this particular study.			●			●	●			-		-	B
350	TK	Ross, Matthew S; Wong, Charles S; Martin, Jonathan W	Isomer-specific biotransformation of perfluorooctane sulfonamide in Sprague-Dawley rats	2012	Environ Sci Technol. 2012 Mar 20;46(6):3196-203. doi: 10.1021/es204028v. Epub 2012 Mar 6.	Great variability exists in perfluorooctane sulfonate (PFOS) isomer patterns in human and wildlife samples, including unexpectedly high percentages (e.g., >40%) of branched isomers in human sera. Previous in vitro tests showed that branched PFOS-precursors were biotransformed faster than the corresponding linear isomer. Thus, high percentages of branched PFOS may be a biomarker of PFOS-precursor exposure in humans. We evaluated this hypothesis by examining the isomer-specific fate of perfluorooctane sulfonamide (PFOSA), a known PFOS-precursor, in male Sprague-Dawley rats exposed to commercial PFOSA via food for 77 days (83.0 ± 20.4 ng kg(-1) day(-1)), followed by 27 days of depuration. Elimination half-lives of the two major branched PFOSA isomers (2.5 ± 1.0 days and 3.7 ± 1.2 days) were quicker than for linear PFOSA (5.9 ± 4.6 days), resulting in a depletion of branched PFOSA isomers in blood and tissues relative to the dose. A corresponding increase in the total branched isomer content of PFOS, the ultimate metabolite, in rat serum was not observed. However, a significant enrichment of 5m-PFOS and a significant depletion of 1m-PFOS were observed, relative to authentic electrochemical PFOS. The data cannot be directly extrapolated to humans, due to known differences in the toxicokinetics of PFOS in rodents and humans. However, the results confirm that in vivo exposure to commercially relevant PFOS-precursors can result in a distinct PFOS isomer profile that may be useful as a biomarker of exposure source.			●							-		C	B
351	TK	Russell, Mark H; Nilsson, Helena; Buck, Robert C	Elimination kinetics of perfluorohexanoic acid in humans and comparison with mouse, rat and monkey	2013	Chemosphere. 2013 Nov;93(10):2419-25. doi: 10.1016/j.chemosphere.2013.08.060. Epub 2013 Sep 16.	Major fluorinated chemical manufacturers have developed new short-chain per- and polyfluorinated substances with more favorable environmental, health and safety profiles. This study provides the first evaluation of the elimination half-life of perfluorohexanoic acid (PFHxA) from the blood of humans. PFHxA biomonitoring data were obtained from a recently published study of professional ski wax technicians. These data were analyzed to provide estimates of the apparent half-life of PFHxA from humans, and comparisons were made with kinetic studies of PFHxA elimination from mice, rats and monkeys. The apparent elimination half-life of PFHxA in highly exposed humans ranged between 14 and 49 d with a geomean of 32 d. The half-lives of PFHxA in mice, rats, monkeys and humans were proportional to body weight with no differences observed between genders, indicating similar volumes of distribution and similar elimination mechanisms among mammalian species. Compared to long-chain perfluoroalkyl acid analogs, PFHxA is rapidly cleared from biota. The consistent weight-normalized elimination half-lives for PFHxA in mammalian species indicates that results obtained from animal models are suitable for establishment of PFHxA benchmark dose and reference dose hazard endpoints for use in human risk assessments.			●							-		C	B
352	TK	Sundström, Maria; Ehresman, David J; Bignert, Anders; Butenhoff, John L; Olsen, Geary W; Chang, Shu-Ching; Bergman, Ake	A temporal € trend study (1972-2008) of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in pooled human milk samples from Stockholm, Sweden	2011	Environ Int. 2011 Jan;37(1):178-83. doi: 10.1016/j.envint.2010.08.014. Epub 2010 Sep 28.	The widespread presence of perfluorooctanesulfonate (PFOS), perfluorooctanoate (PFOA), and perfluorohexanesulfonate (PFHxS) in human general populations and their slow elimination profiles have led to renewed interest in understanding the potential human neonatal exposures of perfluoroalkyls (PFAs) from consumption of human milk. The objective of this study was to evaluate the concentrations of PFOS, PFHxS, and PFOA in pooled human milk samples obtained in Sweden between 1972 and 2008 (a period representing the most significant period of PFA production) and to see whether the time trend of these analytes parallels that indicated in human serum. Chemical analysis of PFOS, PFHxS, and PFOA was performed on pooled Swedish human milk samples from 1972 to 2008 after methodological refinements. The 20 samples which formed the 2007 pool were also analyzed individually to evaluate sample variations. Analyses were performed by HPLC-MS/MS. Due to the complexities of the human milk matrix and the requirement to accurately quantitate low pg/mL concentrations, meticulous attention must be paid to background contamination if accurate results are to be obtained. PFOS was the predominant analyte present in the pools and all three analytes showed statistically significant increasing trends from 1972 to 2000, with concentrations reaching a plateau in the 1990s. PFOA and PFOS showed statistically significant decreasing trends during 2001-2008. At the end of the study, in 2008, the measured concentrations of PFOS, PFHxS, and PFOA in pooled human milk were 75 pg/mL, 14 pg/mL, and 74 pg/mL, respectively. The temporal concentration trends of PFOS, PFHxS, and PFOA observed in human milk are parallel to those reported in the general population serum concentrations.			●	●	●					-		B	B
353	TK	Sundström, Maria; Chang, Shu-Ching; Noker, Patricia E; Gorman, Gregory S; Hart, Jill A; Ehresman, David J; Bergman, Åke; Butenhoff, John L	Comparative pharmacokinetics of perfluorohexanesulfonate (PFHxS) in rats, mice, and monkeys	2012	Reprod Toxicol. 2012 Jul;33(4):441-451. doi: 10.1016/j.reprotox.2011.07.004. Epub 2011 Aug 11.	Perfluorohexanesulfonate (PFHxS) has been found in biological samples from wildlife and humans. The human geometric mean serum PFHxS elimination half-life has been estimated to be 2665days. A series of studies was undertaken to establish pharmacokinetic parameters for PFHxS in rats, mice, and monkeys after single administration with pharmacokinetic parameters determined by WinNonlin(®) software. Rats and mice appeared to be more effective at eliminating PFHxS than monkeys. With the exception of female rats, which had serum PFHxS elimination half-life of approximately 2 days, the serum elimination half-lives in the rodent species and monkeys approximated 1month and 4months, respectively, when followed over extended time periods (10-24weeks). Collectively, these studies provide valuable insight for human health risk assessment regarding the potential for accumulation of PFHxS in humans.			●	●			●			-		B	B
354	TK	Tatum-Gibbs, Katoria; Wambaugh, John F; Das, Kaberi P; Zehr, Robert D; Strynar, Mark J; Lindstrom, Andrew B; Delinsky, Amy; Lau, Christopher	Comparative pharmacokinetics of perfluorononanoic acid in rat and mouse	2011	Toxicology. 2011 Mar 15;281(1-3):48-55. doi: 10.1016/j.tox.2011.01.003. Epub 2011 Jan 13.	Perfluorononanoic acid (PFNA) is a fluorinated organic chemical found at low levels in the environment, but is detectable in humans and wildlife. The present study compared the pharmacokinetic properties of PFNA in two laboratory rodent species. Male and female Sprague-Dawley rats were given a single dose of PFNA by oral gavage at 1, 3, or 10mg/kg, and blood was collected from the tail vein at 1, 2, 3, 4, 7, 16, 21, 28, 35, 42 and 50 days after treatment. In addition, livers and kidneys were collected for PFNA analysis at the terminal time point. CD-1 mice were given a single oral dose of PFNA of 1 or 10mg/kg, and 4 males and 4 females were killed at similar time intervals; trunk blood, liver and kidney were collected. Serum and tissue concentrations of PFNA were determined by LC-MS/MS. Serum elimination of PFNA is by and large linear with exposure doses in the rat; however, like PFOA, a major sex difference in the rate of elimination is observed, with an estimated half-life of 30.6 days for males and 1.4 days for females. PFNA is stored preferentially in the liver but not in the kidneys. In the mouse, the rates of PFNA serum elimination are non-linear with exposure dose and are slightly faster in females than males, with terminal estimated serum half-life of 25.8-68.4 days and 34.3-68.9 days, respectively. PFNA is also stored preferentially in the mouse liver but not in the kidneys. Hepatic uptake appears to be more efficient and storage capacity greater in male mice than in females. These data suggest that (1) PFNA is more persistent in the mouse than in the rat; (2) there is a major sex difference in the serum elimination of PFNA in the rat, but much less so in the mouse; and (3) there is a significantly higher hepatic accumulation of PFNA in male mice than in females.			●	●						-		B	C
355	TK	Vanden Heuvel, J P; Kuslikis, B I; Peterson, R E	Covalent binding of perfluorinated fatty acids to proteins in the plasma, liver and testes of rats	1992	Chem Biol Interact. 1992 May;82(3):317-28. doi: 10.1016/0009-2797(92)90003-4.	Perfluorinated fatty acids alter hepatic lipid metabolism and are potent peroxisome proliferators in rodents. Two such perfluorinated acids, perfluorodecanoic acid (PFDA) and perfluorooctanoic acid (PFOA), were examined to determine if they covalently bind cellular proteins. PFDA and PFOA were found to covalently bind proteins when administered to rats in vivo. The liver, plasma and testes of male rats treated with [1-14C]PFDA or PFOA (9.4 mumol/kg) contained detectable levels of covalently bound 14C (0.1-0.5% of the tissue 14C content). Characterization of PFDA covalent binding to albumin in vitro showed that cysteine significantly decreased binding with no effect of methionine, suggesting protein sulfhydryl groups are involved. In cytosolic and microsomal incubation there was no effect of the addition of CoA, ATP or NADPH on the magnitude of the covalent binding of PFDA. Therefore PFDA need not be metabolically activated to form covalent adducts. Despite demonstration of covalent binding of PFDA and PFOA to proteins both in vivo and in vitro, the role of this macromolecular binding in perfluorinated fatty acid toxicity is not known.			●	●						-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
356	TK	Xie, Wei; Wu, Qian; Kania-Korwel, Izabela; Tharappel, Job C; Telu, Sanjay; Coleman, Mitchell C; Glauert, Howard P; Kannan, Kurunthachalam; Mariappan, S V S; Spitz, Douglas R; Weydert, Jamie; Lehmler, Hans-Joachim	Subacute exposure to N-ethyl perfluorooctanesulfonamidoethanol results in the formation of perfluorooctanesulfonate and alters superoxide dismutase activity in female rats	2009	Arch Toxicol. 2009 Oct;83(10):909-24. doi: 10.1007/s00204-009-0450-y. Epub 2009 Jun 21.	Perfluorooctanesulfonamides, such as N-ethyl perfluorooctanesulfonamidoethanol (N-EtFOSE), are large scale industrial chemicals but their disposition and toxicity are poorly understood despite significant human exposure. The hypothesis that subacute exposure to N-EtFOSE, a weak peroxisome proliferator, causes a redox imbalance in vivo was tested using the known peroxisome proliferator, ciprofibrate, as a positive control. Female Sprague-Dawley rats were treated orally with N-EtFOSE, ciprofibrate or corn oil (vehicle) for 21 days, and levels of N-EtFOSE and its metabolites as well as markers of peroxisome proliferation and oxidative stress were assessed in serum, liver and/or uterus. The N-EtFOSE metabolite profile in liver and serum was in good agreement with reported in vitro biotransformation pathways in rats and the metabolite levels decreasing in the order perfluorooctanesulfonate >> perfluorooctanesulfonamide ~ N-ethyl perfluorooctanesulfonamidoacetate >> perfluorooctanesulfonamidoethanol approximately N-EtFOSE. Although N-EtFOSE treatment significantly decreased the growth rate, increased relative liver weight and activity of superoxide dismutases (SOD) in liver and uterus (total SOD, CuZnSOD and MnSOD), a metabolic study revealed no differences in the metabolome in serum from N-EtFOSE-treated and control animals. Ciprofibrate treatment increased liver weight and peroxisomal acyl Co-A oxidase activity in the liver and altered antioxidant enzyme activities in the uterus and liver. According to NMR metabolomic studies, ciprofibrate treated animals had altered serum lipid profiles compared to N-EtFOSE-treated and control animals, whereas putative markers of peroxisome proliferation in serum were not affected. Overall, this study demonstrates the biotransformation of N-EtFOSE to PFOS in rats that is accompanied by N-EtFOSE-induced alterations in antioxidant enzyme activity.			●							-		B	B
357	TK	Xu, Lin; Krenitsky, Daria M; Seacat, Andrew M; Butenhoff, John L; Anders, M W	Biotransformation of N-Ethyl-N-(2-hydroxyethyl) perfluorooctane sulfonamide by Rat Liver Microsomes, Cytosol, and Slices and by Expressed Rat and Human Cytochromes P450	2004	Chem Res Toxicol. 2004 Jun;17(6):767-75. doi: 10.1021/tx034222x.	Perfluorooctanesulfonic acid (PFOS) and its derivatives have been used in a range of industrial and commercial applications, including the manufacture of surfactants, adhesives, anticorrosion agents, and insecticides. PFOS is found at detectable concentrations in human and wildlife tissues and in the global environment. N-Substituted perfluorooctanesulfonamides are believed to be degraded to PFOS and, therefore, contribute to the accumulation of PFOS in the environment. N-Ethyl-N-(2-hydroxyethyl)perfluorooctanesulfonamide (N-EtFOSE) is converted to PFOS in experimental animals. The objective of this study was to elucidate the pathways for the biotransformation of N-EtFOSE, which is a major precursor and component of PFOS-based compounds. N-EtFOSE and several putative metabolites were incubated with liver microsomes and cytosol and with liver slices from male Sprague-Dawley rats. Microsomal fractions fortified with NADPH catalyzed the N-deethylation of N-EtFOSE to give N-(2-hydroxyethyl)perfluorooctanesulfonamide (FOSE alcohol) and of FOSE alcohol to give perfluorooctanesulfonamide (FOSA). These N-dealkylation reactions were catalyzed mainly by male rat P450 2C11 and P450 3A2 and by human P450 2C19 and 3A4/5. Rat liver microsomal fractions incubated with UDP-glucuronic acid catalyzed the O-glucuronidation of N-EtFOSE and FOSE alcohol and the N-glucuronidation of FOSA. Cytosolic fractions incubated with NAD(+) catalyzed the oxidation of FOSE alcohol to perfluooctanesulfonamidoacetate (FOSAA). The oxidation of N-EtFOSE to N-ethylperfluorooctanesulfonamidoacetate (N-EtFOSAA) was observed in liver slices but not in cytosolic fractions. FOSA was biotransformed in liver slices to PFOS, albeit at a low rate. These results show that the major pathway for the biotransformation of N-EtFOSE is N-dealkylation to give FOSA. The biotransformation of FOSA to PFOS explains the observation that PFOS is found in animals given N-EtFOSE.			●							-		B	B
358	TK	Zhang, Tao; Sun, Hongwen; Lin, Yan; Qin, Xiaolei; Zhang, Yanfeng; Geng, Xia; Kannan, Kurunthachalam	Distribution of poly- and perfluoroalkyl substances in matched samples from pregnant women and carbon chain length related maternal transfer	2013	Environ Sci Technol. 2013 Jul 16;47(14):7974-81. doi: 10.1021/es400937y. Epub 2013 Jul 2.	Although levels of poly- and perfluoroalkyl substances (PFASs) in human maternal and neonatal blood have been widely reported in the literature, relationship of maternal-fetal transmission of PFASs with carbon chain length is presently not well understood. In this study, 11 PFASs were analyzed in matched samples, including not only maternal blood (MB, n = 31) and cord blood (CB, n = 30), but also placenta (n = 29) and amniotic fluid (AF, n = 29). Except for perfluorohexanoic acid (PFHxA), the detection frequencies of PFASs were similar among placenta, MB, and CB (>80% for 8 PFASs, nondetectable for 2 PFASs). Though only perfluorooctanoic acid (PFOA) was frequently detected (>90%) in AF, with a median concentration of 0.043 ng/mL, other 5 PFASs were also detectable in AF samples with low concentrations (mean: 0.013-0.191 ng/mL). This suggests that in addition to blood-borne in utero exposure, the fetus is also exposed to low levels of PFASs through AF. Concentrations of PFOA in AF were positively correlated with those in MB ($r = 0.738$, $p < 0.01$) and CB ($r = 0.683$, $p < 0.001$), suggesting that AF concentration could reflect fetal PFOA exposure during pregnancy and can be used as a biomarker. To clarify the effects of carbon chain length on maternal transfer of PFASs, we calculated maternal transfer efficiencies of PFASs from MB to CB (TMB-CB). A U-shaped trend in TMB-CB of C7-C12 perfluoroalkyl carboxylic acids (PFCAs) with increasing carbon chain length was found in this study for the first time. The U-shaped TMB-CB of PFCAs with carbon chain length is an integrated result of opposite trend of the ratios between MB/placenta and placenta/CB based on carbon chain length. This is the first study to report the occurrence of PFASs in human placenta. The results reported here enable better understanding of the maternal-fetal transmission of PFASs.		●	●						●	-	1	A	A
359	TK	Campbell, J.L., Jr. and Clewell, H.J., III.	Report on the perfluorooctanesulfonic acid (PFOS) kinetic models and dosimetry	2013	Final contract report to Health Canada.	No abstract available					●				企業データ		D	D
360	TK	Campbell, J.L., Jr. and Clewell, H.J. III.	Report on the perfluorooctanoic acid (PFOA) kinetic models and dosimetry	2013	Final contract report to Health Canada.	No abstract available						●			企業データ		D	D
361	PBPK	Bernstein, A. S.; Kapraun, D. F.; Schlosser, P. M.	A Model Template Approach for Rapid Evaluation and Application of Physiologically Based Pharmacokinetic Models for Use in Human Health Risk Assessments: A Case Study on Per- and Polyfluoroalkyl Substances	2021	Toxicol Sci. 2021 Aug 3;182(2):215-228. doi: 10.1093/toxsci/kfab063.	Physiologically based pharmacokinetic (PBPK) models are commonly used in risk assessments to perform inter- and intraspecies extrapolations as well as to extrapolate between different dosing scenarios; however, they must first undergo quality assurance review, which can be a time-consuming process, especially when model code is not readily available. We developed and implemented (using R and MCSim) a PBPK model template capable of replicating published model results for several chemical-specific PBPK models. This model template allows for faster quality assurance review because the general model equations only need to be reviewed once, and application to a specific chemical then only requires reviewing input parameters. The model template can implement PBPK models with oral and intravenous exposure routes, varying numbers of tissue compartments, renal reabsorption, and multiple elimination pathways, including fecal, urinary, and biliary. Using the model template, we reproduced published model simulation results for perfluorohexanesulfonic acid, perfluorononanoic acid, perfluorodecanoic acid, perfluorooctanoate, and perfluorooctane sulfonate. We also show that the template can be a useful tool for identifying potential model errors. Thus, the model template allows for faster evaluation and review of published PBPK models and provides a proof of concept for using this approach with broader classes of chemical-specific PBPK models.	●	●								-		B	A
362	PBPK	Brochot, C.; Casas, M.; Manzano-Salgado, C.; Zeman, F. A.; Schettgen, T.; Vrijheid, M.; Bois, F. Y.	Prediction of maternal and foetal exposures to perfluoroalkyl compounds in a Spanish birth cohort using toxicokinetic modelling	2019	Toxicol Appl Pharmacol. 2019 Sep 15;379:114640. doi: 10.1016/j.taap.2019.114640.	Prenatal exposures to perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) have been associated with child health outcomes, but many of these associations remain poorly characterized. The aim of this work was to provide new indicators of foetal exposure for the Spanish INMA birth cohort. First, a pregnancy and lactation physiologically based pharmacokinetic (PBPK) model was calibrated in a population framework to provide quantitative estimates for the PFOA and PFOS placental transfers in humans. The estimated distributions indicated that PFOA crosses the placental barrier at a rate three times higher than PFOS and shows a higher variability between mothers. The PBPK model was then used to back-calculate the time-varying daily intakes of the INMA mothers corrected for their individual history from a spot maternal concentration. We showed the importance of accounting for the mothers' history as different dietary intakes can result in similar measured concentrations at one time point. Finally, the foetal exposure was simulated in target organs over pregnancy using the PBPK model and the estimated maternal intakes. We showed that the pattern of PFOA and PFOS exposures varies greatly among the foetuses. About a third has levels of either one compound always higher than the levels of the other compound. The other two thirds showed different ranking of PFOA and PFOS in terms of concentrations in the target organs. Our simulated foetal exposures bring additional information to the measured maternal spot concentrations and can help to better characterize the prenatal exposure in target organs during windows of susceptibility.	●	●								-		B	B
363	PBPK	Cheng, W.; Ng, C. A.	A permeability-limited physiologically based pharmacokinetic (PBPK) model for perfluorooctanoic acid (PFOA) in male rats	2017	Environ Sci Technol. 2017 Sep 5;51(17):9930-9939. doi: 10.1021/acs.est.7b02602. Epub 2017 Aug 18.	Physiologically based pharmacokinetic (PBPK) modeling is a powerful in silico tool that can be used to simulate the toxicokinetics and tissue distribution of xenobiotic substances, such as perfluorooctanoic acid (PFOA), in organisms. However, most existing PBPK models have been based on the flow-limited assumption and largely rely on in vivo data for parametrization. In this study, we propose a permeability-limited PBPK model to estimate the toxicokinetics and tissue distribution of PFOA in male rats. Our model considers the cellular uptake and efflux of PFOA via both passive diffusion and transport facilitated by various membrane transporters, association with serum albumin in circulatory and extracellular spaces, and association with intracellular proteins in liver and kidney. Model performance is assessed using seven experimental data sets extracted from three different studies. Comparing model predictions with these experimental data, our model successfully predicts the toxicokinetics and tissue distribution of PFOA in rats following exposure via both IV and oral routes. More importantly, rather than requiring in vivo data fitting, all PFOA-related parameters were obtained from in vitro assays. Our model thus provides an effective framework to test in vitro-in vivo extrapolation and holds great promise for predicting toxicokinetics of per- and polyfluorinated alkyl substances in humans.	●	●		●						-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献クラン①抽出	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
364	PBPK	Chou, W. C.; Lin, Z.	Development of a Gestational and Lactational Physiologically Based Pharmacokinetic (PBPK) Model for Perfluorooctane Sulfonate (PFOS) in Rats and Humans and Its Implications in the Derivation of Health-Based Toxicity Values	2021	Environ Health Perspect. 2021 Mar;129(3):37004. doi: 10.1289/EHP7671. Epub 2021 Mar 17.	BACKGROUND: There is a great concern on potential adverse effects of exposure to perfluorooctane sulfonate (PFOS) in sensitive subpopulations, such as pregnant women, fetuses, and neonates, due to its reported transplacental and lactational transfer and reproductive and developmental toxicities in animals and humans.OBJECTIVES: This study aimed to develop a gestational and lactational physiologically based pharmacokinetic (PBPK) model in rats and humans for PFOS to aid risk assessment in sensitive human subpopulations.METHODS: Based upon existing PBPK models for PFOS, the present model addressed a data gap of including a physiologically based description of basolateral and apical membrane transporter-mediated renal reabsorption and excretion in kidneys during gestation and lactation. The model was calibrated with published rat toxicokinetic and human biomonitoring data and was independently evaluated with separate data. Monte Carlo simulation was used to address the interindividual variability.RESULTS: Model simulations were generally within 2-fold of observed PFOS concentrations in maternal/fetal/neonatal plasma and liver in rats and humans. Estimated fifth percentile human equivalent doses (HEDs) based on selected critical toxicity studies in rats following U.S. Environmental Protection Agency (EPA) guidelines ranged from 0.08 to . These values are lower than the HEDs estimated in U.S. EPA guidance () using an empirical toxicokinetic model in adults.CONCLUSIONS: The results support the importance of renal reabsorption/excretion during pregnancy and lactation in PFOS dosimetry and suggest that the derivation of health-based toxicity values based on developmental toxicity studies should consider gestational/lactational dosimetry estimated from a life stage-appropriate PBPK model. This study provides a quantitative tool to aid risk reevaluation of PFOS, especially in sensitive human subpopulations, and it provides a basis for extrapolating to other per- and polyfluoroalkyl substances (PFAS). All model codes and detailed tutorials are provided in the Supplemental Materials to allow readers to reproduce our results and to use this model.	●	●							●	-		A	B
365	PBPK	Corley, RA; Mendrala, AL; Smith, FA; Staats, DA; Gargas, ML; Conolly, RB; Andersen, ME; Reitz, RH.	Development of a physiologically based pharmacokinetic model for chloroform	1990	Toxicol Appl Pharmacol. 1990 May;103(3):512-27. doi: 10.1016/0041-008x(90)90324-n.	A physiologically based pharmacokinetic model describing the disposition of chloroform in mice, rats, and humans was developed. This model was designed to facilitate extrapolations from high doses, such as those used in chronic rodent studies, to low doses that humans may be exposed to in the workplace or the environment. Kinetic constants for mice and rats were derived from in vivo experiments. Enzymatic studies conducted with samples of rodent and human tissues provided a rational basis for estimating human in vivo metabolic rate constants. Incorporation of physiological descriptions of the processes of absorption, distribution, metabolism, and excretion allowed extrapolation between different routes of exposure as well. The model was validated by comparing model predictions with experimental data gathered in mice, rats, and humans after inhalation, oral, or intraperitoneal administration of chloroform. Consistent with previous reports, the metabolic activation of chloroform to toxic intermediates was shown to occur most rapidly in the mouse, less rapidly in the rat, and most slowly in humans. Estimates of the "delivered dose" of chloroform metabolites to internal organs sensitive to chloroform toxicity were calculated. This model may be used to develop refined dose estimates for human populations exposed to low levels of chloroform in the environment.	●	●								-		C	C
366	PBPK	Lorber, M.; Egeghy, P. P.	An assessment of the exposure of Americans to perfluorooctane sulfonate: A comparison of estimated intake with values inferred from NHANES data	2011	Environ Sci Technol. 2011 Oct 1;45(19):8006-14. doi: 10.1021/es103718h. Epub 2011 Apr 25.	Models for assessing intakes of perfluorooctanoic acid, PFOA, are described and applied. One model is based on exposure media concentrations and contact rates. This model is applied to general population exposures for adults and 2-year old children. The other model is a simple one-compartment, first-order pharmacokinetic (PK) model. Parameters for this model include a rate of elimination of PFOA and a blood volume of distribution. The model was applied to data from the National Health and Nutritional Examination Survey, NHANES, to backcalculate intakes. The central tendency intake estimate for adults and children based on exposure media concentrations and contact rates were 70 and 26 ng/day, respectively. The central tendency adult intake derived from NHANES data was 56 and 37 ng/day for males and females, respectively. Variability and uncertainty discussions regarding the intake modeling focus on lack of data on direct exposure to PFOA used in consumer products, precursor compounds, and food. Discussions regarding PK modeling focus on the range of blood measurements in NHANES, the appropriateness of the simple PK model, and the uncertainties associated with model parameters. Using the PK model, the 10th and 95th percentile long-term average adult intakes of PFOA are 15 and 130 ng/day.	●	●		●						-		B	A
367	PBPK	Fàbrega, F.; Kumar, V.; Schuhmacher, M.; Domingo, J. L.; Nadal, M.	PBPK modeling for PFOS and PFOA: validation with human experimental data	2014	Toxicol Lett. 2014 Oct 15;230(2):244-51. doi: 10.1016/j.toxlet.2014.01.007. Epub 2014 Jan 17.	In recent years, because of the potential human toxicity, concern on perfluoroalkyl substances (PFASs) has increased notably with special attention to perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS). Unfortunately, there is currently an important knowledge gap on the burdens of these chemicals in most human tissues, as the reported studies have been mainly focused on plasma. In order to overcome these limitations, the use of physiologically-based pharmacokinetic (PBPK) models has been extended. The present study was aimed at testing an existing PBPK model for their predictability of PFOS and PFOA in a new case-study, and also to adapt it to estimate the PFAS content in human tissue compartments. Model validation was conducted by means of PFOA and PFOS concentrations in food and human drinking water from Tarragona County (Catalonia, Spain), and being the predicted results compared with those experimentally found in human tissues (blood, liver, kidney, liver and brain) of subjects from the same area of study. The use of human-derived partition coefficient (Pk) data was proven as more suitable for application to this PBPK model than rat-based Pk values. However, the uncertainty and variability of the data are still too high to get conclusive results. Consequently, further efforts should be carried out to reduce parametric uncertainty of PBPK models. More specifically, a deeper knowledge on the distribution of PFOA and PFOS within the human body should be obtained by enlarging the number of biological monitoring studies on PFASs.	●	●		●						-		B	B
368	PBPK	Janků, I, .	Physiological modelling of renal drug clearance	1993	Eur J Clin Pharmacol. 1993;44(6):513-9. doi: 10.1007/BF02440850.	A physiological model of renal drug clearance is presented with the aim of establishing a basis for adjusting drug dosing regimens in renal insufficiency. In agreement with the morphology of blood supply to the nephron, the model assumes serial arrangement of the processes involved in drug excretion. Fractional extraction by filtration in the glomeruli is defined in terms of the product of the unbound fraction of the drug, the filtration fraction being responsible for the limited extraction efficiency of this process. For a description of the limitations of the tubular secretory process by plasma flow through peritubular capillaries, the parallel tube model is utilized. The assumption of direct proportionality between the transport maximum of the secretory process and filtrate flow in the tubules permits a quantitative comparison of the intrinsic tubular secretion clearance and the effectiveness of the filtration process. Provided that the secretory mechanism is highly effective, renal clearance becomes dependent only on kidney plasma flow and the fraction of drug not reabsorbed in the tubules. Tubular reabsorption results only in a proportional decrease in renal clearance. The model predicts proportionality of renal drug clearance to GFR, which as a rule is used for dosage adjustment of drugs in renal insufficiency, only for compounds exclusively excreted by filtration. Compounds also excreted by tubular secretion in general exhibit a curvilinear relationship. The curvature is less pronounced as an increasing fraction of the drug is protein bound in blood. Therefore, for dosage adjustment of drugs secreted in the tubules and highly bound in blood, proportionality between renal clearance and GFR can serve as a reasonable approximation. According to the model, distinct deviations from simple proportionality, which will require dosage adjustment methods involving assessment both of glomerular and tubular functions of the kidney, can be expected mainly for drugs for which an efficient flow-dependent secretion process is not counteracted by extensive binding of the drug to blood constituents.	●	●								-		C	C
369	PBPK	Kim, S.; Choi, K.; Ji, K.; Seo, J.; Kho, Y.; Park, J.; Kim, S.; Park, S.; Hwang, I.; Jeon, J.; Yang, H.; Giesy, J. P.	Trans-placental transfer of thirteen perfluorinated compounds and relations with fetal thyroid hormones	2011	Environ Sci Technol. 2011 Sep 1;45(17):7465-72. doi: 10.1021/es202408a. Epub 2011 Aug 12.	While the results of animal studies have shown that perfluorinated compounds (PFCs) can modulate concentrations of thyroid hormones in blood, limited information is available on relationships between concentrations of PFCs in human blood serum and fetal thyroid hormones. The relationship between concentrations of PFCs in blood and fetal thyroid hormone concentrations or birth weight, and ratios of major PFCs between maternal and fetal serum were determined. Concentrations of PFCs were measured in blood serum of pregnant women (n = 44), fetal cord blood serum (n = 43) and breast milk (n = 35). Total concentrations of thyroxin (T4), triiodothyronin (T3) and thyroid stimulating hormone (TSH) in blood serum were also quantified. The ratios of major PFCs in maternal versus fetal serum were 1:1.93, 1.02, 0.72, and 0.48 for perfluorotridecanoic acid (PFTrDA), perfluorooctanoic acid (PFOA), perfluorohexane sulfonate (PFHxS), and perfluorooctane sulfonate (PFOS), respectively. Fetal PFOS, PFOA, PFTrDA and maternal PFTrDA were correlated with fetal total T4 concentrations, but after adjusting for major covariates, most of the relationships were no longer statistically significant. However, the significant negative correlations between maternal PFOS and fetal T3, and maternal PFTrDA and fetal T4 and T3 remained. Since thyroid hormones are crucial in the early development of the fetus, its clinical implication should be evaluated. Given the observed trans-placental transfer of PFCs, efforts should be also made to elucidate the exposure sources among pregnant women.	●	●	●		●	●	●			-	1	-	A
370	ADME	Wambaugh, JF; Setzer, RW; Pitruzzello, AM; Liu, J; Reif, DM; Kleinstreuer, NC; Wang, NC; Sipes, N; Martin, M; Das, K; Dewitt, JC; Strynar, M; Judson, R; Houck, KA; Lau, C.	Dosimetric anchoring of in vivo and in vitro studies for perfluorooctanoate and perfluorooctanesulfonate.	2013	Toxicol Sci. 136: 308-327. doi: 10.1093/toxsci/kft204. Epub 2013 Sep 17.	In order to compare between in vivo toxicity studies, dosimetry is needed to translate study-specific dose regimens into dose metrics such as tissue concentration. These tissue concentrations may then be compared with in vitro bioactivity assays to perhaps identify mechanisms relevant to the lowest observed effect level (LOEL) dose group and the onset of the observed in vivo toxicity. Here, we examine the perfluorinated compounds (PFCs) perfluorooctanoate (PFOA) and perfluorooctanesulfonate (PFOS). We analyzed 9 in vivo toxicity studies for PFOA and 13 in vivo toxicity studies for PFOS. Both PFCs caused multiple effects in various test species, strains, and genders. We used a Bayesian pharmacokinetic (PK) modeling framework to incorporate data from 6 PFOA PK studies and 2 PFOS PK studies (conducted in 3 species) to predict dose metrics for the in vivo LOELs and no observed effect levels (NOELs). We estimated PK parameters for 11 combinations of chemical, species, strain, and gender. Despite divergent study designs and species-specific PK, for a given effect, we found that the predicted dose metrics corresponding to the LOELs (and NOELs where available) occur at similar concentrations. In vitro assay results for PFOA and PFOS from EPA's ToxCast project were then examined. We found that most in vitro bioactivity occurs at concentrations lower than the predicted concentrations for the in vivo LOELs and higher than the predicted concentrations for the in vivo NOELs (where available), for a variety of nonimmunological effects. These results indicate that given sufficient PK data, the in vivo LOELs dose regimens, but not necessarily the effects, could have been predicted from in vitro studies for these 2 PFCs.	●	●		●		●	●		●	-	1	A	A

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
371	ADME	Loccisano, A. E.; Longnecker, M. P.; Campbell, J. L., Jr; Andersen, M. E.; Clewell, H. J., III	Development of pbpk models for pfoa and pfos for human pregnancy and lactation life stages	2013	J Toxicol Environ Health A. 2013;76(1):25-57. doi: 10.1080/15287394.2012.722523.	Perfluoroalkyl acid carboxylates and sulfonates (PFAA) have many consumer and industrial applications. Developmental toxicity studies in animals have raised concern about potential reproductive/developmental effects of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS); however, in humans conflicting results have been reported for associations between maternal PFAA levels and these outcomes. Risk assessments and interpretation of available human data during gestation and lactation are hindered due to lack of a framework for understanding and estimating maternal, fetal, and neonatal pharmacokinetics (PK). Physiologically based pharmacokinetic (PBPK) models were developed for PFOA and PFOS for the gestation and lactation life stages in humans to understand how the physiological changes associated with development affect pharmacokinetics of these compounds in the mother, fetus, and infant. These models were derived from PBPK models for PFOA/PFOS that were previously developed for adult humans and rats during gestation and lactation and from existing human pregnancy and lactation models developed for other chemicals. The models simulated PFOA and PFOS concentrations in fetal, infant, and maternal plasma and milk, were compared to available data in humans, and also were used to estimate maternal exposure. The models reported here identified several research needs, which include -1 the identification of transporters involved in renal resorption to explain the multiyear half-lives of these compounds in humans, -2 factors affecting clearance of PFOA/PFOS during gestation and lactation, and -3 data to estimate clearance of PFOA/PFOS in infants. These models may help address concerns regarding possible adverse health effects due to PFOA/PFOS exposure in the fetus and infant and may be useful in comparing pharmacokinetics across life stages.	●	●	●	●	●	●			-	1	A	A
372	ADME	Verner, M. A.; Ngueta, G.; Jensen, E. T.; Fromme, H.; Völkel, W.; Nygaard, U. C.; Granum, B.; Longnecker, M. P.	A simple pharmacokinetic model of prenatal and postnatal exposure to perfluoroalkyl substances (PFASs)	2016	Environ Sci Technol. 2016 Jan 19;50(2):978-86. doi: 10.1021/acs.est.5b04399. Epub 2016 Jan 6.	Most children are exposed to perfluoroalkyl substances (PFASs) through placental transfer, breastfeeding, and other environmental sources. To date, there are no validated tools to estimate exposure and body burden during infancy and childhood. In this study, we aimed to (i) develop a two-generation pharmacokinetic model of prenatal and postnatal exposure to perfluorooctanoic acid (PFOA), perfluorooctanesulfonate (PFOS), and perfluorohexanesulfonate (PFHxS); and to (ii) evaluate it against measured children's levels in two studies. We developed a pharmacokinetic model consisting of a maternal and a child compartment to simulate lifetime exposure in women and transfer to the child across the placenta and through breastfeeding. To evaluate the model, we performed simulations for each mother-child dyad from two studies in which maternal PFAS levels at delivery and children's PFAS levels were available. Model predictions based on maternal PFAS levels, sex of child, body weight, and duration of breastfeeding explained between 0.52 and 0.6 of the variability in measured children's levels at 6 months of age and between 0.52 and 0.62 at 36 months. Monte Carlo simulations showed that the daily intake through breastfeeding and resulting internal PFAS levels can be much higher in nursing infants than in mothers. This pharmacokinetic model shows potential for postnatal exposure assessment in the context of epidemiological studies and risk assessment.	●	●		●					●	-	1	A	A
373	ADME	Loccisano, Anne E; Campbell, Jerry L Jr; Andersen, Melvin E; Clewell, Harvey J 3rd	Evaluation and prediction of pharmacokinetics of PFOA and PFOS in the monkey and human using a PBPK model	2011	Regul Toxicol Pharmacol. 2011 Feb;59(1):157-75. doi: 10.1016/j.yrtph.2010.12.004.	Perfluoroalkyl acid carboxylates and sulfonates (PFAAs) have many consumer and industrial applications. The persistence and widespread distribution of these compounds in humans have brought them under intense scrutiny. Limited pharmacokinetic data is available in humans; however, human data exists for two communities with drinking water contaminated by PFAAs. Also, there is toxicological and pharmacokinetic data for monkeys, which can be quite useful for cross-species extrapolation to humans. The goal of this research was to develop a physiologically-based pharmacokinetic (PBPK) model for PFOA and PFOS for monkeys and then scale this model to humans in order to describe available human drinking water data. The monkey model simulations were consistent with available PK data for monkeys. The monkey model was then extrapolated to the human and then used to successfully simulate the data collected from residents of two communities exposed to PFOA in drinking water. Human PFOS data is minimal; however, using the half-life estimated from occupational exposure, our model exhibits reasonable agreement with the available human serum PFOS data. It is envisioned that our PBPK model will be useful in supporting human health risk assessments for PFOA and PFOS by aiding in understanding of human pharmacokinetics.		●	●	●	●	●			●	No. 370と重複、削除予定	1	A	A
374	PBPK	Theurich, Melissa A; Davanzo, Riccardo; Busck-Rasmussen, Marianne; Díaz-Gómez, N Marta; Brennan, Christine; Kylberg, Elisabeth; Bærug, Anne; McHugh, Laura; Weikert, Cornelia; Abraham, Klaus; Koletzko, Berthold	Breastfeeding rates and programs in europe: a survey of 11 national breastfeeding committees and representatives	2019	J Pediatr Gastroenterol Nutr. 2019 Mar;68(3):400-407. doi: 10.1097/MPG.0000000000002234.	INTRODUCTION: Among the world's regions, the WHO European Region has the lowest rates of exclusive breastfeeding at the age of 6 months with approximately 25%. Low rates and early cessation of breastfeeding have important adverse health consequences for women, infants, and young children. Protecting, promoting, and supporting breastfeeding are a public health priority. OBJECTIVES: National breastfeeding data and monitoring systems among selected European countries and the WHO European Region are compared. Mechanisms for the support, protection, and promotion of breastfeeding are reviewed and successes and challenges in implementation of national programs are presented. METHODS: National representatives of national breastfeeding committees and initiatives in 11 European countries, including Belgium, Croatia, Denmark, Germany, Ireland, Italy, The Netherlands, Norway, Spain, Sweden, and Switzerland, participated in a standardized survey. Results are evaluated and compared in a narrative review. RESULTS: Variation exists in Europe on breastfeeding rates; methodology for data collection; and mechanisms for support, protection, and promotion of breastfeeding. Directly after birth, between 56% and 98% of infants in all countries were reported to receive any human milk, and at 6 months 38% to 71% and 13% to 39% of infants to be breastfed or exclusively breastfed, respectively. National plans addressing breastfeeding promotion, protection, and support exist in 6 of the 11 countries. CONCLUSIONS: National governments should commit to evidence-based breastfeeding monitoring and promotion activities, including financial and political support, to improve breastfeeding rates in the Europe. Renewed efforts for collaboration between countries in Europe, including a sustainable platform for information exchange, are needed.			●							-		C	C
375	PBPK	Allen, B C; Covington, T R; Clewell, H J	Investigation of the impact of pharmacokinetic variability and uncertainty on risks predicted with a pharmacokinetic model for chloroform	1996	Toxicology. 1996 Jul 17;111(1-3):289-303. doi: 10.1016/0300-483x(96)03383-5.	A sensitivity and uncertainty analysis was performed on the Reitz et al. (Toxicol. Appl. Pharmacol., 1990: 105, 443) physiologically based pharmacokinetic (PBPK) risk assessment model for chloroform. The analytical approach attempted to separately consider the impacts of interindividual variability and parameter uncertainty on the predicted values of the dose metrics in the model, as well as on liver cancer risk estimates obtained with the model. An important feature of the analytical approach was that an attempt was made to incorporate information on correlation between important parameters, for example, the observed correlation between total blood flow and alveolar ventilation rate. Using the published PBPK model for chloroform, the best estimate of the average population risk based on the preferred pharmacodynamic dose metric (PTDEAD), representing cell death, is 9.2 x 10(-7); this estimate is more than 500-fold lower than the risk estimate of 5.3 x 10(-4) based on an alternative pharmacokinetic dose metric (AVEMMB), which represents tissue adduct formation. However, when interindividual variability was considered the range of individual risks (from the 5th to the 95th percentile of the population) predicted with PTDEAD was extremely broad (from 3.0 x 10(-13) to 3.2 x 10(-4)), while individual risks predicted with AVEMMB only varied over a factor of four (from 1.9 x 10(-4) to 7.4 x 10(-4)). As a result, the upper 95th percentile of the distribution of individual risk estimates based on the preferred cell death metric were within a factor of three of the 95th percentile for the pharmacokinetic alternative. The crucial factor with respect to the much greater variability of chloroform risk estimates based on cell death is that the dose metric, PTDEAD, is exquisitely sensitive to variation of the parameters in the model defining the response of cells to the cytotoxicity of chloroform. Unfortunately, these key parameters are also highly uncertain, as well as strongly correlated. As a result it proved impossible to accurately quantify the additional impact of parameter uncertainty on the dose metrics and risk estimates for chloroform. In general, however, the approach used in this study should be useful for differentiating the impact of interindividual variability and parameter uncertainty on PBPK-based risk assessments of other chemicals where the sensitivity, uncertainty, and correlation of the key parameters are more limited.				●						-		C	C
376	PBPK	Brochot, Céline; Smith, Thomas J; Bois, Frédéric Y	Development of a physiologically based toxicokinetic model for butadiene and four major metabolites in humans: Global sensitivity analysis for experimental design issues	2007	Chem Biol Interact. 2007 May 1;167(3):168-83. doi: 10.1016/j.cbi.2007.02.010. Epub 2007 Feb 21.	1,3-Butadiene (BD) is metabolized in humans and rodents to mutagenic and carcinogenic species. Our previous work has focused on developing a physiologically based toxicokinetic (PBTK) model for BD to estimate its metabolic rate to 1,2-epoxy-3-butene (EB), using exhaled breath BD concentrations in human volunteers exposed by inhalation. In this paper, we extend our BD model to describe the kinetics of its four major metabolites EB, 1,2:3,4-diepoxybutane (DEB), 3-butene-1,2-diol (BDD), and 3,4-epoxy-1,2-butanediol (EBD), and to test whether the extended model and experimental data (to be collected for BD and metabolites in humans) are together adequate to estimate the metabolic rate constants of each of the above chemicals. Global sensitivity analyses (GSA) were conducted to evaluate the relative importance of the model parameters on model outputs during the 20min of exposure and the 40min after exposure ended. All model parameters were studied together with various potentially measurable model outputs: concentrations of BD and EB in exhaled air, concentrations of BD and all metabolites in venous blood, and cumulated amounts of urinary metabolites excreted within 24h. Our results show that pulmonary absorption of BD and subsequent distribution and metabolism in the well-perfused tissues compartment are the critical processes in the toxicokinetics of BD and metabolites. In particular, three parameters influence numerous outputs: the blood:air partition coefficient for BD, the metabolic rate of BD to EB, and the volume of the well-perfused tissues. Other influential parameters include other metabolic rates, some partition coefficients, and parameters driving the gas exchanges (in particular, for BD outputs). GSA shows that the impact of the metabolic rate of BD to EB on the BD concentrations in exhaled air is greatly increased if a few of the model's important parameters (such as the blood:air partition coefficient for BD) are measured experimentally. GSA also shows that all the transformation pathways described in the PBTK model may not be estimable if only data on the studied outputs are collected, and that data on a specific output for a chemical may not inform all the transformations involving that chemical.				●						-		C	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
377	PBPK	Fàbrega, Francesc; Nadal, Martí; Schuhmacher, Marta; Domingo, José L; Kumar, Vikas	Influence of the uncertainty in the validation of PBPK models: A case-study for PFOS and PFOA	2016	Regul Toxicol Pharmacol. 2016 Jun;77:230-9. doi: 10.1016/j.yrtph.2016.03.009. Epub 2016 Mar 15.	Physiologically-based pharmacokinetic (PBPK) models are mathematical representations of the human body aimed at describing the time course distribution of chemicals in human tissues. Since parameterization of PBPK models is based on empirical estimation and experimental data, simulation results may have high degree of uncertainty. As a consequence, the reliability of model validation is highly affected. In this study, the parametric uncertainty associated with PBPK models developed for perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) were analyzed and the different validation approaches were discussed for a case-study in Tarragona County (NE of Spain). Physicochemical parameters and dietary intake of PFOS and PFOA were estimated from previous investigations performed in Tarragona County. A sensitivity analysis (SA) was performed to understand the degree of influence of input parameters on the final outcomes. The uncertainty of the PBPK models' outcome was assessed by propagating the parametric uncertainty using the Latin Hypercube Sampling (LHS) technique. The elimination constants (Tm and Kt) as well as the Free fraction and the Intake, were the most influential parameters according to the SA results, being up to 83% for PFOS and 99.9% for PFOA. The validation of the PBPK model, which was performed using different approaches, showed clear discrepancies in the visual validation when compared with the statistical analysis.				●						-		B	B
378	PBPK	Krishnan K, Andersen ME, Clewell HJ, et al.	Physiologically based pharmacokinetic modeling of chemical mixtures	1994	San Diego, CA: Academic Press, 399-437.	No abstract available				●						-		D	D
379	PBPK	Rodriguez, Chester E; Setzer, R Woodrow; Barton, Hugh A	Pharmacokinetic modeling of perfluorooctanoic acid during gestation and lactation in the mouse	2009	Reprod Toxicol. 2009 Jun;27(3-4):373-386. doi: 10.1016/j.reprotox.2009.02.009. Epub 2009 Mar 4.	Perfluorooctanoic acid (PFOA) is a processing aid for the polymerization of commercially valuable fluoropolymers. Its widespread environmental distribution, presence in human blood, and adverse effects in animal toxicity studies have triggered attention to its potential adverse effects to humans. PFOA is not metabolized and exhibits dramatically different serum/plasma half-lives across species. Estimated half-lives for humans, monkeys, mice, and female rats are 3-5 years, 20-30 days, 12-20 days, and 2-4h, respectively. Developmental toxicity is one of the most sensitive adverse effects associated with PFOA exposure in rodents, but its interpretation for risk assessment is currently hampered by the lack of understanding of the inter-species pharmacokinetics of PFOA. To address this uncertainty, a biologically supported dynamic model was developed whereby a two-compartment system linked via placental blood flow described gestation and milk production linked a lactating dam to a growing pup litter compartment. Postnatal serum levels of PFOA for 129S1/SvImJ mice at doses of 1mg/kg or less were reasonably simulated while prenatal and postnatal measurements for CD-1 mice at doses of 1mg/kg or greater were simulated via the addition of a biologically based saturable renal resorption description. Our results suggest that at low doses a linear model may suffice for describing the pharmacokinetics of PFOA while a more complex model may be needed at higher doses. Although mice may appear more sensitive based on administered dose of PFOA, the internal dose metrics estimated in this analysis indicate that they may be equal or less sensitive than rats.				●						-		B	B
380	PBPK	Sweeney, L M; Tyler, T R; Kirman, C R; Corley, R A; Reitz, R H; Paustenbach, D J; Holson, J F; Whorton, M D; Thompson, K M; Gargas, M L	Proposed occupational exposure limits for select ethylene glycol ethers using PBPK models and Monte Carlo simulations	2001	Toxicol Sci. 2001 Jul;62(1):124-39. doi: 10.1093/toxsci/62.1.124.	Methoxyethanol (ethylene glycol monomethyl ether, EGME), ethoxyethanol (ethylene glycol monoethyl ether, EGEE), and ethoxyethyl acetate (ethylene glycol monoethyl ether acetate, EGEEA) are all developmental toxicants in laboratory animals. Due to the imprecise nature of the exposure data in epidemiology studies of these chemicals, we relied on human and animal pharmacokinetic data, as well as animal toxicity data, to derive 3 occupational exposure limits (OELs). Physiologically based pharmacokinetic (PBPK) models for EGME, EGEE, and EGEEA in pregnant rats and humans have been developed (M. L. Gargas et al., 2000, Toxicol. Appl. Pharmacol. 165, 53-62; M. L. Gargas et al., 2000, Toxicol. Appl. Pharmacol. 165, 63-73). These models were used to calculate estimated human-equivalent no adverse effect levels (NAELs), based upon internal concentrations in rats exposed to no observed effect levels (NOELs) for developmental toxicity. Estimated NAEL values of 25 ppm for EGEEA and EGEE and 12 ppm for EGME were derived using average values for physiological, thermodynamic, and metabolic parameters in the PBPK model. The uncertainties in the point estimates for the NOELs and NAELs were estimated from the distribution of internal dose estimates obtained by varying key parameter values over expected ranges and probability distributions. Key parameters were identified through sensitivity analysis. Distributions of the values of these parameters were sampled using Monte Carlo techniques and appropriate dose metrics calculated for 1600 parameter sets. The 95th percentile values were used to calculate interindividual pharmacokinetic uncertainty factors (UFs) to account for variability among humans (UF(h,pk)). These values of 1.8 for EGEEA/EGEE and 1.7 for EGME are less than the default value of 3 for this area of uncertainty. The estimated human equivalent NAELs were divided by UF(h,pk) and the default UFs for pharmacodynamic variability among animals and among humans to calculate the proposed OELs. This methodology indicates that OELs (8-h time-weighted average) that should protect workers from the most sensitive adverse effects of these chemicals are 2 ppm EGEEA and EGEE (11 mg/m(3) EGEEA, 7 mg/m(3) EGEE) and 0.9 ppm (3 mg/m(3)) EGME. These recommendations assume that dermal exposure will be minimal or nonexistent.				●						-		C	C
381	PBPK	Wambaugh, John F; Barton, Hugh A; Setzer, R Woodrow	Comparing models for perfluorooctanoic acid pharmacokinetics using Bayesian analysis	2008	J Pharmacokinet Pharmacodyn. 2008 Dec;35(6):683-712. doi: 10.1007/s10928-008-9108-2. Epub 2009 Jan 8.	Selecting the appropriate pharmacokinetic (PK) model given the available data is investigated for perfluorooctanoic acid (PFOA), which has been widely analyzed with an empirical, one-compartment model. This research examined the results of experiments [Kemper R. A., DuPont Haskell Laboratories, USEPA Administrative Record AR-226.1499 (2003)] that administered single oral or iv doses of PFOA to adult male and female rats. PFOA concentration was observed over time; in plasma for some animals and in fecal and urinary excretion for others. There were four rats per dose group, for a total of 36 males and 36 females. Assuming that the PK parameters for each individual within a gender were drawn from the same, biologically varying population, plasma and excretion data were jointly analyzed using a hierarchical framework to separate uncertainty due to measurement error from actual biological variability. Bayesian analysis using Markov Chain Monte Carlo (MCMC) provides tools to perform such an analysis as well as quantitative diagnostics to evaluate and discriminate between models. Starting from a one-compartment PK model with separate clearances to urine and feces, the model was incrementally expanded using Bayesian measures to assess if the expansion was supported by the data. PFOA excretion is sexually dimorphic in rats; male rats have bi-phasic elimination that is roughly 40 times slower than that of the females, which appear to have a single elimination phase. The male and female data were analyzed separately, keeping only the parameters describing the measurement process in common. For male rats, including excretion data initially decreased certainty in the one-compartment parameter estimates compared to an analysis using plasma data only. Allowing a third, unspecified clearance improved agreement and increased certainty when all the data was used, however a significant amount of eliminated PFOA was estimated to be missing from the excretion data. Adding an additional PK compartment reduced the unaccounted-for elimination to amounts comparable to the cage wash. For both sexes, an MCMC estimate of the appropriateness of a model for a given data type, the Deviance Information Criterion, indicated that this two-compartment model was better suited to describing PFOA PK. The median estimate was 142.1 +/- 37.6 ml/kg for the volume of the primary compartment and 1.24 +/- 1.1 ml/kg/h for the clearances of male rats and 166.4 +/- 46.8 ml/kg and 30.3 +/- 13.2 ml/kg/h, respectively for female rats. The estimates for the second compartment differed greatly with gender-volume 311.8 +/- 453.9 ml/kg with clearance 3.2 +/- 6.2 for males and 1400 +/- 2507.5 ml/kg and 4.3 +/- 2.2 ml/kg/h for females. The median estimated clearance was 12 +/- 6% to feces and 85 +/- 7% to urine for male rats and 8 +/- 6% and 77 +/- 9% for female rats. We conclude that the available data may support more models for PFOA PK beyond two-compartments and that the methods employed here will be generally useful for more complicated, including PBPK, models.				●						-		B	B
382	PBPK	Worley, Rachel Rogers; Fisher, Jeffrey	Application of physiologically-based pharmacokinetic modeling to explore the role of kidney transporters in renal reabsorption of perfluorooctanoic acid in the rat	2015	Toxicol Appl Pharmacol. 2015 Dec 15;289(3):428-41. doi: 10.1016/j.taap.2015.10.017. Epub 2015 Nov 6.	Renal elimination and the resulting clearance of perfluorooctanoic acid (PFOA) from the serum exhibit pronounced sex differences in the adult rat. The literature suggests that this is largely due to hormonally regulated expression of organic anion transporters (OATs) on the apical and basolateral membranes of the proximal tubule cells that facilitate excretion and reabsorption of PFOA from the filtrate into the blood. Previously developed PBPK models of PFOA exposure in the rat have not been parameterized to specifically account for transporter-mediated renal elimination. We developed a PBPK model for PFOA in male and female rats to explore the role of Oat1, Oat3, and Oatp1a1 in sex-specific renal reabsorption and excretion of PFOA. Descriptions of the kinetic behavior of these transporters were extrapolated from in vitro studies and the model was used to simulate time-course serum, liver, and urine data for intravenous (IV) and oral exposures in both sexes. Model predicted concentrations of PFOA in the liver, serum, and urine showed good agreement with experimental data for both male and female rats indicating that in vitro derived physiological descriptions of transporter-mediated renal reabsorption can successfully predict sex-dependent excretion of PFOA in the rat. This study supports the hypothesis that sex-specific serum half-lives for PFOA are largely driven by expression of transporters in the kidney and contribute to the development of PBPK modeling as a tool for evaluating the role of transporters in renal clearance.				●						-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報抽出対象	文献ランク①	文献ランク②
383	PBPK	Kapraun, Dustin F; Zurlinden, Todd J; Verner, Marc-Andre; Chiang, Catheryne; Dzierlenga, Michael W; Carlson, Laura M; Schlosser, Paul M; Lehmann, Geniece M	Pharmacokinetic Models for Quantifying Mother-to-Offspring Transfer of Lipophilic Persistent Environmental Chemicals	2022	Toxicol Sci. 2022 Sep 24;189(2):155-174. doi: 10.1093/toxsci/kfac084.	Lipophilic persistent environmental chemicals (LPECs) can accumulate in a woman's body and transfer to her developing child across the placenta and via breast milk. To assess health risks associated with developmental exposures to LPECs, we developed a pharmacokinetic (PK) model that quantifies mother-to-offspring transfer of LPECs during pregnancy and lactation and facilitates internal dosimetry calculations for offspring. We parameterized the model for mice, rats, and humans using time-varying functions for body mass and milk consumption rates. The only required substance-specific parameter is the elimination half-life of the LPEC in the animal species of interest. We used the model to estimate whole-body concentrations in mothers and offspring following maternal exposures to hexachlorobenzene (HCB) and 2,2',4,4',5,5'-hexachlorobiphenyl (PCB 153) and compared these with measured concentrations from animal studies. We also compared estimated concentrations for humans to those generated using a previously published human LPEC PK model. Finally, we compared human equivalent doses (HEDs) calculated using our model and an allometric scaling method. Estimated and observed whole-body concentrations of HCB and PCB 153 in offspring followed similar trends and differed by less than 60%. Simulations of human exposure yielded concentration estimates comparable to those generated using the previously published model, with concentrations in offspring differing by less than 12%. HEDs calculated using our PK model were about 2 orders of magnitude lower than those generated using allometric scaling. Our PK model can be used to calculate internal dose metrics for offspring and corresponding HEDs and thus informs assessment of developmental toxicity risks associated with LPECs.		●								-		C	C
384	PBPK	Clewell, H.	Pharmacokinetic modeling of PFOA and PFOS, USEPA, Washington DC	2019	Environ Health Perspect. 128: 27006.	No abstract available						●				-		D	D
385	PBPK	Chou, Wei-Chun; Lin, Zhoumeng	Probabilistic human health risk assessment of perfluorooctane sulfonate (PFOS) by integrating in vitro, in vivo toxicity, and human epidemiological studies using a Bayesianbased dose-response assessment coupled with physiologically based pharmacokinetic (PBPK) modeling approach	2020	Environ Int. 2020 Apr;137:105581. doi: 10.1016/j.envint.2020.105581. Epub 2020 Feb 19.	BACKGROUND: Environmental exposure to perfluorooctane sulfonate (PFOS) is associated with various adverse outcomes in humans. However, risk assessment for PFOS with the traditional risk estimation method is faced with multiple challenges because there are high variabilities and uncertainties in its toxicokinetics and toxicity between species and among different types of studies. OBJECTIVES: This study aimed to develop a robust probabilistic risk assessment framework accounting for interspecies and inter-experiment variabilities and uncertainties to derive the human equivalent dose (HED) and reference dose for PFOS. METHODS: A Bayesian dose-response model was developed to analyze selected 34 critical studies, including human epidemiological, animal in vivo, and ToxCast in vitro toxicity datasets. The dose-response results were incorporated into a multi-species physiologically based pharmacokinetic (PBPK) model to reduce the toxicokinetic/toxicodynamic variabilities. In addition, a population-based probabilistic risk assessment of PFOS was performed for Asian, Australian, European, and North American populations, respectively, based on reported environmental exposure levels. RESULTS: The 5th percentile of HEDs derived from selected studies was estimated to be 21.5 (95% CI: 10.6-36.3) ng/kg/day. After exposure to environmental levels of PFOS, around 50% of the population in all studied populations would likely have >20% of increase in serum cholesterol, but the effects on other endpoints were estimated to be minimal (<10% changes). There was a small population (~10% of the population) that was highly sensitive to endocrine disruption and cellular response by environmental PFOS exposure. CONCLUSION: Our results provide insights into a complete risk characterization of PFOS and may help regulatory agencies in the reevaluation of PFOS risk. Our new probabilistic approach can conduct dose-response analysis of different types of toxicity studies simultaneously and this method could be used to improve risk assessment for other perfluoroalkyl substances (PFAS).									●	-		B	B
386	PBPK	US EPA (Environmental Protection Agency)	Recommended Use of Body Weight ¾ as the Default Method in Derivation of the Oral Reference Dose	2011	EPA/100/R11/0001, https://www.epa.gov/sites/default/files/2013-09/documents/recommended-use-of-bw34.pdf	No abstract available									●	EPAガイダンス		D	D
387	環境中運命	Buck, R. C.; Franklin, J.; Berger, U.; Conder, J. M.; Cousins, I. T.; de Voogt, P.; Jensen, A. A.; Kannan, K.; Mabury, S. A.; van Leeuwen, S. P.	Perfluoroalkyl and polyfluoroalkyl substances in the environment: terminology, classification, and origins [Review]	2011	Integr Environ Assess Manag. 2011 Oct;7(4):513-41. doi: 10.1002/ieam.258.	The primary aim of this article is to provide an overview of perfluoroalkyl and polyfluoroalkyl substances (PFASs) detected in the environment, wildlife, and humans, and recommend clear, specific, and descriptive terminology, names, and acronyms for PFASs. The overarching objective is to unify and harmonize communication on PFASs by offering terminology for use by the global scientific, regulatory, and industrial communities. A particular emphasis is placed on long-chain perfluoroalkyl acids, substances related to the long-chain perfluoroalkyl acids, and substances intended as alternatives to the use of the long-chain perfluoroalkyl acids or their precursors. First, we define PFASs, classify them into various families, and recommend a pragmatic set of common names and acronyms for both the families and their individual members. Terminology related to fluorinated polymers is an important aspect of our classification. Second, we provide a brief description of the 2 main production processes, electrochemical fluorination and telomerization, used for introducing perfluoroalkyl moieties into organic compounds, and we specify the types of byproducts (isomers and homologues) likely to arise in these processes. Third, we show how the principal families of PFASs are interrelated as industrial, environmental, or metabolic precursors or transformation products of one another. We pay particular attention to those PFASs that have the potential to be converted, by abiotic or biotic environmental processes or by human metabolism, into long-chain perfluoroalkyl carboxylic or sulfonic acids, which are currently the focus of regulatory action. The Supplemental Data lists 42 families and subfamilies of PFASs and 268 selected individual compounds, providing recommended names and acronyms, and structural formulas, as well as Chemical Abstracts Service registry numbers.	●	●	●	●	●	●				-		D	-
388	環境中運命	Higgins, Christopher P; Luthy, Richard G	Sorption of perfluorinated surfactants on sediments	2006	Environ Sci Technol. 2006 Dec 1;40(23):7251-6. doi: 10.1021/es061000n.	The sorption of anionic perfluorochemical (PFC) surfactants of varying chain lengths to sediments was investigated using natural sediments of varying iron oxide and organic carbon content. Three classes of PFC surfactants were evaluated for sorptive potential: perfluorocarboxylates, perfluorosulfonates, and perfluorooctyl sulfonamide acetic acids. PFC surfactant sorption was influenced by both sediment-specific and solution-specific parameters. Sediment organic carbon, rather than sediment iron oxide content, was the dominant sediment-parameter affecting sorption, indicating the importance of hydrophobic interactions. However, sorption also increased with increasing solution [Ca2+] and decreasing pH, suggesting that electrostatic interactions play a role. Perfluorocarbon chain length was the dominant structural feature influencing sorption, with each CF2 moiety contributing 0.50-0.60 log units to the measured distribution coefficients. The sulfonate moiety contributed an additional 0.23 log units to the measured distribution coefficient, when compared to carboxylate analogs. In addition, the perfluorooctyl sulfonamide acetic acids demonstrated substantially stronger sorption than perfluorooctane sulfonate (PFOS). These data should prove useful for modeling the environmental fate of this class of contaminants.	●	●	●	●	●	●			●	-		B	-
389	環境中運命	Ahrens, Lutz; Bundschuh, Mirco	Fate and effects of poly- and perfluoroalkyl substances in the aquatic environment: a review.	2014	Environ Toxicol Chem. 2014 Sep;33(9):1921-9. doi: 10.1002/etc.2663. Epub 2014 Jul 31.	Polyfluoroalkyl and perfluoroalkyl substances (PFASs) are distributed ubiquitously in the aquatic environment, which raises concern for the flora and fauna in hydrosystems. The present critical review focuses on the fate and adverse effects of PFASs in the aquatic environment. The PFASs are continuously emitted into the environment from point and nonpoint sources such as sewage treatment plants and atmospheric deposition, respectively. Although concentrations of single substances may be too low to cause adverse effects, their mixtures can be of significant environmental concern. The production of C8 -based PFASs (i.e., perfluorooctane sulfonate [PFOS] and perfluorooctanoate [PFOA]) is largely phased out; however, the emissions of other PFASs, in particular short-chain PFASs and PFAS precursors, are increasing. The PFAS precursors can finally degrade to persistent degradation products, which are, in particular, perfluoroalkane sulfonates (PFSAs) and perfluoroalkyl carboxylates (PFCAs). In the environment, PFSAs and PFCAs are subject to partitioning processes, whereby short-chain PFSAs and PFCAs are mainly distributed in the water phase, whereas long-chain PFSAs and PFCAs tend to bind to particles and have a substantial bioaccumulation potential. However, there are fundamental knowledge gaps about the interactive toxicity of PFAS precursors and their persistent degradation products but also interactions with other natural and anthropogenic stressors. Moreover, because of the continuous emission of PFASs, further information about their ecotoxicological potential among multiple generations, species interactions, and mixture toxicity seems fundamental to reliably assess the risks for PFASs to affect ecosystem structure and function in the aquatic environment.			●							-		B	-
390	環境中運命	Ahrens, Lutz; Yeung, Leo W Y; Taniyasu, Sachi; Lam, Paul K S; Yamashita, Nobuyoshi	Partitioning of perfluorooctanoate (PFOA), perfluorooctane sulfonate (PFOS) and perfluorooctane sulfonamide (PFOSA) between water and sediment.	2011	Chemosphere. 2011 Oct;85(5):731-7. doi: 10.1016/j.chemosphere.2011.06.046. Epub 2011 Jul 13.	Laboratory partitioning experiments were conducted to elucidate the sorption behaviour and partitioning of perfluoroalkyl compounds (PFCs). Three different sediment types were used and separately spiked with perfluorooctanoate (PFOA), perfluorooctane sulfonate (PFOS) and perfluorooctane sulfonamide (PFOSA) at low environmentally realistic concentrations. PFOA, PFOS and PFOSA were mainly distributed in the dissolved phase at low suspended solid concentrations, indicating their long-range transport potential in the marine environment. In all cases, the equilibrium isotherms were linear and the organic carbon normalised partition coefficients (K(OC)) decreased in the following order: PFOSA (log K(OC) = 4.1 ± 0.35 $cm^3 g^{-1}$)>PFOS (3.7 ± 0.56 $cm^3 g^{-1}$) > PFOA (2.4 ± 0.12 $cm^3 g^{-1}$). The level of organic content had a significant influence on the partitioning. For the sediment with negligible organic content the density of the sediment became the most important factor influencing the partitioning. Ultimately, data on the partitioning of PFCs between aqueous media and suspended solids are essential for modelling their transport and environmental fate.			●							-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献ランク①	文献ランク②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
391	環境中運命	D'Eon, Jessica C; Mabury, Scott A	Production of perfluorinated carboxylic acids (PFCAs) from the biotransformation of polyfluoroalkyl phosphate surfactants (PAPS): exploring routes of human contamination	2007	Environ Sci Technol. 2007 Jul 1;41(13):4799-805. doi: 10.1021/es070126x.	Perfluorinated acids are detected in human blood world-wide, with increased levels observed in industrialized areas. The origin of this contamination is not well understood. A possible route of exposure, which has received little attention experimentally, is indirect exposure to perfluorinated acids through ingestion of chemicals applied to food contact paper packaging. The current investigation quantified the load of perfluorinated acids to Sprague-Dawley rats upon exposure to polyfluoroalkyl phosphate surfactants (PAPS), nonpolymeric fluorinated surfactants approved for application to food contact paper products. The animals were administered a single dose at 200 mg/kg by oral gavage of 8:2 fluorotelomer alcohol (8:2 FTOH) mono-phosphate (8:2 monoPAPS), or the corresponding di-phosphate (8:2 diPAPS), with blood taken over 15 days post-dosing to monitor uptake, biotransformation, and elimination. Upon completion of the time-course study the animals were redosed using an identical dosing procedure, with sacrifice and necropsy 24 h after the second dosing. Increased levels of perfluorooctanoic acid (PFOA), along with both 8:2 PAPS congeners, were observed in the blood of the dosed animals. In the 8:2 monoPAPS-dosed animals, 8:2 monoPAPS and PFOA blood concentrations peaked at 7900 +/- 1200 ng/g and 34 +/- 4 ng/g respectively. In the 8:2 diPAPS-dosed animals, 8:2 diPAPS peaked in concentration at 32 +/- 6 ng/g, and 8:2 monoPAPS and PFOA peaked at 900 +/- 200 ng/g and 3.8 +/- 0.3 ng/g, respectively. Several established polyfluorinated metabolites previously identified in 8:2 FTOH metabolism studies were also observed in the dosed animals. Consistent with other fluorinated contaminants, the tissue distributions showed increased levels of both PFOA and the 8:2 PAPS congeners in the liver relative to the other tissues measured. Previous investigations have found that PAPS can migrate into food from paper packaging. Here we link ingestion of PAPS with in vivo production of perfluorinated acids.			●	●						-		B	-
392	環境中運命	Ellis, David A; Martin, Jonathan W; De Silva, Amila O; Mabury, Scott A; Hurley, Michael D; Sulbaek Andersen, Mads P; Wallington, Timothy J	Degradation of fluorotelomer alcohols: a likely atmospheric source of perfluorinated carboxylic acids	2004	Environ Sci Technol. 2004 Jun 15;38(12):3316-21. doi: 10.1021/es049860w.	Human and animal tissues collected in urban and remote global locations contain persistent and bioaccumulative perfluorinated carboxylic acids (PFCAs). The source of PFCAs was previously unknown. Here we present smog chamber studies that indicate fluorotelomer alcohols (FTOHs) can degrade in the atmosphere to yield a homologous series of PFCAs. Atmospheric degradation of FTOHs is likely to contribute to the widespread dissemination of PFCAs. After their bioaccumulation potential is accounted for, the pattern of PFCAs yielded from FTOHs could account for the distinct contamination profile of PFCAs observed in arctic animals. Furthermore, polar bear liver was shown to contain predominately linear isomers (>99%) of perfluorononanoic acid (PFNA), while both branched and linear isomers were observed for perfluorooctanoic acid, strongly suggesting a sole input of PFNA from "telomer"-based products. The significance of the gas-phase peroxy radical cross reactions that produce PFCAs has not been recognized previously. Such reactions are expected to occur during the atmospheric degradation of all polyfluorinated materials, necessitating a reexamination of the environmental fate and impact of this important class of industrial chemicals.			●	●		●				-		B	-
393	環境中運命	Kissa E	Fluorinated surfactants and repellents, 2nd Edition	2001	Surfactant Science Series, Volume 97. Marcel Dekker Inc., New York, 623 pp. ISBN: 0-8247-0472-X	No abstract available			●							書籍		D	-
394	環境中運命	Land, M.; de Wit, C. A.; Bignert, A.; Cousins, I.; Herzke, D.; Johansson, J. H.; Martin, J. W.	What is the effect of phasing out long-chain per- and polyfluoroalkyl substances on the concentrations of perfluoroalkyl acids and their precursors in the environment	2018	Environmental Evidence. volume 7, Article number: 4 (2018), doi: 10.1186/s13750-017-0114-y	Background: There is a concern that continued emissions of man-made per-and polyfluoroalkyl substances (PFASs) may cause environmental and human health effects. Now widespread in human populations and in the environment, several PFASs are also present in remote regions of the world, but the environmental transport and fate of PFASs are not well understood. Phasing out the manufacture of some types of PFASs started in 2000 and further regulatory and voluntary actions have followed. The objective of this review is to understand the effects of these actions on global scale PFAS concentrations.Methods: Searches for primary research studies reporting on temporal variations of PFAS concentrations were performed in bibliographic databases, on the internet, through stakeholder contacts and in review bibliographies. No time, document type, language or geographical constraints were applied in the searches. Relevant subjects included human and environmental samples. Two authors screened all retrieved articles. Dual screening of 0.1 of the articles was performed at title/abstract and full-text levels by all authors. Kappa tests were used to test consistency. Relevant articles were critically appraised by four reviewers, with double checking of 0.2 of the articles by a second reviewer. Meta-analysis of included temporal trends was considered but judged to not be appropriate. The trends were therefore discussed in a narrative synthesis.Results: Available evidence suggests that human concentrations of perfluorooctane sulfonate (PFOS), perfluorodecane sulfonate (PFDS), and perfluorooctanoic acid (PFOA) generally are declining, while previously increasing concentrations of perfluorohexane sulfonate (PFHxS) have begun to level off. Rapid declines for PFOS-precursors (e.g. perfluorooctane sulfonamide, FOSA) have also been consistently observed in human studies. In contrast, limited data indicate that human concentrations of PFOS and PFOA are increasing in China where the production of these substances has increased. Human concentrations of longer-chained perfluoroalkyl carboxylic acids (PFCAs) with 44818 carbon atoms are generally increasing or show insignificant trends with too low power to detect a trend. For abiotic and biological environmental samples there are no clear patterns of declining trends. Most substances show mixed results, and a majority of the trends are insignificant with low power to detect a trend.Conclusions: For electrochemically derived PFASs, including PFOS and PFOA, most human studies in North America and Europe show consistent statistically significant declines. This contrasts with findings in wildlife and in abiotic environmental samples, suggesting that declining PFOS, PFOS-precursor and PFOA concentrations in humans likely resulted from removal of certain PFASs from commercial products including paper and board			●							-		B	-
395	環境中運命	Lee, Holly; D'eon, Jessica; Mabury, Scott A	Biodegradation of polyfluoroalkyl phosphates as a source of perfluorinated acids to the environment	2010	Environ Sci Technol. 2010 May 1;44(9):3305-10. doi: 10.1021/es9028183.	Wastewater treatment plants (WWTPs) have been identified as a major source of perfluorocarboxylates (PFCAs) to aqueous environments. The observed increase in PFCA mass flows from WWTP influent to effluent suggests the biodegradation of commercial fluorinated materials within the WWTP. Commercial fluorinated surfactants are used as greaseproofing agents in food-contact paper products as well as leveling and wetting agents. As WWTPs are likely the major fate of these surfactants, their biodegradation may be a source of PFCA production. One class of commercial surfactants, the polyfluoroalkyl phosphates (PAPs), have been observed in WWTP sludge. While PAPs have been shown to degrade into PFCAs in a rat model, the present study investigates their microbial fate to determine whether the biodegradation of PAPs within a WWTP-simulated system will contribute to the load of PFCAs released. PAPs are applied commercially in mixed formulations of different chain lengths and substitution at the phosphate center. The effect of chain length and phosphate substitution on the biodegradation of PAPs was investigated by incubating mixtures of 4:2, 6:2, 8:2, and 10:2 monosubstituted PAPs (monoPAPs) in an aerobic microbial system and by separately incubating the 6:2 monoPAP and 6:2 disubstituted PAP (diPAP) for 92 days. Headspace sampling revealed production of the fluorotelomer alcohols (FTOHs) from the hydrolysis of the PAP phosphate ester linkages. Analysis of the aqueous phase revealed microbial transformation of the PAPs to the final PFCA products was possible. The majority of the oxidation products observed were consistent with previous investigations that have suggested fluorotelomer precursor compounds degrade predominantly via a beta-oxidation-like mechanism. However, in this study, the detection of odd-chain PFCAs suggests that other pathways may be important. The present study demonstrated microbially mediated biodegradation of PAPs to PFCAs. This observation, together with the diPAP concentrations observed in WWTP sludge, suggest PAPs-containing commercial products may be a significant contributor to the increased PFCA mass flows observed in WWTP effluents.			●			●				-		C	-
396	植物の取り込み	Stahl, T; Heyn, J; Thiele, H; Hüther, J; Failing, K; Georgii, S; Brunn, H	Carryover of Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS) from Soil to Plants	2009	Arch Environ Contam Toxicol. 2009 Aug;57(2):289-98. doi: 10.1007/s00244-008-9272-9. Epub 2008 Dec 27.	Within the scope of a joint project to study soil-to-plant carryover of polyfluorinated compounds (PFCs), five cultivated plants (spring wheat, oats, potatoes, maize, and perennial ryegrass) were sown or planted in Mitscherlich pots. Six variants per species were used, each with a different concentration level of PFOA and PFOS (from 0.25 to 50 mg/kg as aqueous solution) to detect possible concentration dependence in the transfer of these two PFCs from soil to plant. PFOA and PFOS were detected by liquid chromatography-tandem mass spectrometry after appropriate sample preparation (partial drying, mincing, homogenizing, extraction). Since PFOA and PFOS presently represent the most widely studied PFCs, they are classified as "leading compounds." The results show that concentrations of PFOA/PFOS in the plants vary greatly, depending on the concentrations applied to the soil. PFOA values were higher than PFOS values in all plants except potatoes, in which these differences could be quite substantial. From the results presented here it can be seen that uptake and storage are much more intensive in the vegetative portion of the plant than relocation in the storage organs. This is particularly evident from the the comparison of concentrations found in the grain and ear and those in the straw or rest of the plant in spring wheat, oats, and maize. Transfer from "soil to crops" provides a possible explanation for the presence of PFCs in foodstuffs and in human body fluids such as blood, plasma, serum, or breast milk. The aim of the present study was to determine whether a statistically significant, concentration-dependent carryover of PFOA and PFOS in crop plants can take place, which would provide a potential entrance point for these substances into the food chain.			●	●						-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
397	植物の取り込み	Blaine, Andrea C; Rich, Courtney D; Hundal, Lakhwinder S; Lau, Christopher; Mills, Marc A; Harris, Kimberly M; Higgins, Christopher P	Uptake of perfluoroalkyl acids into edible crops via land applied biosolids: Field and greenhouse studies	2013	Environ Sci Technol. 2013 Dec 17;47(24):14062-9. doi: 10.1021/es403094q. Epub 2013 Nov 21.	The presence of perfluoroalkyl acids (PFAAs) in biosolids destined for use in agriculture has raised concerns about their potential to enter the terrestrial food chain via bioaccumulation in edible plants. Uptake of PFAAs by greenhouse lettuce (Lactuca sativa) and tomato (Lycopersicon lycopersicum) grown in an industrially impacted biosolids-amended soil, a municipal biosolids-amended soil, and a control soil was measured. Bioaccumulation factors (BAFs) were calculated for the edible portions of both lettuce and tomato. Dry weight concentrations observed in lettuce grown in a soil amended (biosolids:soil dry weight ratio of 1:10) with PFAA industrially contaminated biosolids were up to 266 and 236 ng/g for perfluorobutanoic acid (PFBA) and perfluoropentanoic acid (PFPeA), respectively, and reached 56 and 211 ng/g for PFBA and PFPeA in tomato, respectively. BAFs for many PFAAs were well above unity, with PFBA having the highest BAF in lettuce (56.8) and PFPeA the highest in tomato (17.1). In addition, the BAFs for PFAAs in greenhouse lettuce decreased approximately 0.3 log units per CF2 group. A limited-scale field study was conducted to verify greenhouse findings. The greatest accumulation was seen for PFBA and PFPeA in both field-grown lettuce and tomato; BAFs for PFBA were highest in both crops. PFAA levels measured in lettuce and tomato grown in field soil amended with only a single application of biosolids (at an agronomic rate for nitrogen) were predominantly below the limit of quantitation (LOQ). In addition, corn (Zea mays) stover, corn grains, and soil were collected from several full-scale biosolids-amended farm fields. At these fields, all PFAAs were below the LOQ in the corn grains and only trace amounts of PFBA and PFPeA were detected in the corn stover. This study confirms that the bioaccumulation of PFAAs from biosolids-amended soils depends strongly on PFAA concentrations, soil properties, the type of crop, and analyte.				●					-		B	-
398	植物の取り込み	Blaine, Andrea C; Rich, Courtney D; Sedlacko, Erin M; Hyland, Katherine C; Stushnoff, Cecil; Dickenson, Eric R V; Higgins, Christopher P	Perfluoroalkyl acid uptake in lettuce (Lactuca sativa) and strawberry (Fragaria ananassa) irrigated with reclaimed water	2014	Environ Sci Technol. 2014 Dec 16;48(24):14361-8. doi: 10.1021/es504150h. Epub 2014 Nov 25.	Using reclaimed water to irrigate food crops presents an exposure pathway for persistent organic contaminants such as perfluoroalkyl acids (PFAAs) to enter the human food chain. This greenhouse study used reclaimed water augmented with varying concentrations (0.2-40 μg/L) of PFAAs, including perfluorocarboxylates (C3F7COO(-) to C8F17COO(-)) and perfluorosulfonates (C4F9SO2O(-), C6F13SO2O(-), C8F17SO2O(-)), to investigate potential uptake and concentration-response trends in lettuce (Lactuca sativa) and strawberry (Fragaria ananassa). In addition, studies were conducted to evaluate the role of soil organic carbon concentrations on plant uptake of PFAAs. PFAA concentrations in lettuce leaves and strawberry fruit were measured for each aqueous PFAA concentration applied. PFAA plant concentrations increased linearly with the aqueous concentration for all PFAAs, with PFCAs bioaccumulating to a greater degree than PFSAs in the edible portions of the tested plants. Chain-length-dependency trends were evident in both lettuce shoot and strawberry fruit, with decreasing concentrations associated with increasing chain length. Perfluorobutanoate (PFBA) and perfluoropentanoate (PFPeA), both short-chain PFAAs (<8 carbon chain length), accumulated the most compared with other PFAAs tested in the edible parts of both lettuce and strawberry. PFAA concentrations in strawberry root and shoot were also measured at selected PFAA aqueous concentrations (0.4, 4, and 40 μg/L). Short-chain perfluorocarboxylates were the dominant fraction in the strawberry fruit and shoot compartments, whereas a more even distribution of all PFAAs appeared in the root compartment. Lettuce grown in soils with varying organic carbon contents (0.4%, 2%, 6%) was used to assess the impact of organic carbon sorption on PFAA bioaccumulation. The lettuce grown in soil with the 6% organic carbon content had the lowest bioaccumulation of PFAAs. Bioaccumulation factors for lettuce were correlated to carbon chain length of PFAAs, showing approximately a 0.4 to 0.6 log decrease per CF2 group. This study confirms that PFAAs can enter and bioaccumulate in food crops irrigated with reclaimed water. Bioaccumulation potential depends on analyte functional group and chain length, concentration in the reclaimed water, and organic carbon content of the soil.				●					-		B	-
399	環境中運命	Dinglasan-Panlilio, Mary Joyce A; Mabury, Scott A	Significant residual fluorinated alcohols present in various fluorinated materials	2006	Environ Sci Technol. 2006 Mar 1;40(5):1447-53. doi: 10.1021/es051619+.	Polyfluorinated telomer alcohols and sulfonamides are classes of compounds recently identified as precursor molecules to the perfluorinated acids detected in the environment. Despite the detection and quantification of these volatile compounds in the atmosphere, their sources remain unknown. Both classes of compounds are used in the synthesis of various fluorosurfactants and incorporated in polymeric materials used extensively in the carpet, textile, and paper industries. This study has identified the presence of residual unbound fluoro telomer alcohols (FTOHs) in varying chain lengths (C6-C14) in several commercially available and industrially applied polymeric and surfactant materials. NMeFOSE, a perfluoroalkyl sulfonamido alcohol, was also detected in a commercially available carpet protector product. A method was developed to remove these residual compounds from polymeric and surfactant materials by dispersion in water and stripping of the volatiles using a constant flow of air and trapping on XAD resin. Using gas chromatography mass spectrometry analysis, it was determined that the fluorinated materials examined consist of 0.04-3.8% residual alcohols on a fluoro alcohol to dry mass basis. These values indicate that residual alcohols, left unreacted and unbound from the manufacturing process of fluorinated polymers and surfactants, could be a significant source of the polyfluorinated telomer alcohols and sulfonamides released into the environment. This study suggests that elimination or reduction of these residual alcohols from all marketed fluorinated polymers and fluorosurfactants is key in reducing the prevalence of perfluorinated acids formed in the environment.				●					-		C	-
400	環境中運命	Krippner, Johanna; Brunn, Hubertus; Falk, Sandy; Georgii, Sebastian; Schubert, Sven; Stahl, Thorsten	Effects of chain length and pH on the uptake and distribution of perfluoroalkyl substances in maize (Zea mays)	2014	Chemosphere. 2014 Jan;94:85-90. doi: 10.1016/j.chemosphere.2013.09.018. Epub 2013 Oct 3.	Maize is the most important grain crop grown for human nutrition, animal fodder and biogas production worldwide. Nonetheless, no systematic studies have been undertaken on these plants to examine the uptake mechanisms for perfluoroalkyl substances (PFASs) dependent upon chain length and pH value. The aim of the present study was therefore to determine the influence of chain length (C4 to C10) and pH value (pH 5, pH 6, pH 7) on the uptake and distribution of seven perfluoroalkyl carboxylic acids (PFCAs) and three perfluoroalkane sulfonic acids (PFSAs) by maize in nutrient solution experiments under controlled conditions in a climate chamber. A pH-dependent uptake was observed for perfluorodecanoic acid (PFDA) with an uptake rate of 2.51 μg g(-1) at pH 5 compared to 1.52 μg g(-1) root dry weight (DW) per day (d) at pH 7. Perfluorobutanoic acid (PFBA) had the highest uptake rate within the group of PFCAs with an average of 2.46 μg g(-1) root DWd(-1) and perfluorooctane sulfonic acid (PFOS) had the highest uptake rate (3.63 μg g(-1) root DWd(-1)) within the group of PFSAs. The shoot:root ratio for shorter-chain PFCAs (≤ C7) and PFBS (C4) was >2.0, which indicates that shorter-chain PFASs are transferred predominantly and at higher concentrations to the shoot. In contrast, long-chain PFCAs such as perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA) and perfluorodecanoic acid (PFDA) as well as the PFASs perfluorohexane sulfonic acid (PFHxS) and perfluorooctane sulfonic acid (PFOS) accumulated at higher concentrations in the roots of maize plants with a shoot:root ratio of <1.0.				●					-		B	-
401	環境中運命	Rahman, Mohammad Feisal; Peldszus, Sigrid; Anderson, William B	Behaviour and fate of perfluoroalkyl and polyfluoroalkyl substances (PFAS) in drinking water treatment: A review	2014	Water Res. 2014 Mar 1;50:318-40. doi: 10.1016/j.watres.2013.10.045. Epub 2013 Oct 26.	This article reviews perfluoroalkyl and polyfluoroalkyl substance (PFAS) characteristics, their occurrence in surface water, and their fate in drinking water treatment processes. PFASs have been detected globally in the aquatic environment including drinking water at trace concentrations and due, in part, to their persistence in human tissue some are being investigated for regulation. They are aliphatic compounds containing saturated carbon-fluorine bonds and are resistant to chemical, physical, and biological degradation. Functional groups, carbon chain length, and hydrophilicity/hydrophobicity are some of the important structural properties of PFASs that affect their fate during drinking water treatment. Full-scale drinking water treatment plant occurrence data indicate that PFASs, if present in raw water, are not substantially removed by most drinking water treatment processes including coagulation, flocculation, sedimentation, filtration, biofiltration, oxidation (chlorination, ozonation, AOPs), UV irradiation, and low pressure membranes. Early observations suggest that activated carbon adsorption, ion exchange, and high pressure membrane filtration may be effective in controlling these contaminants. However, branched isomers and the increasingly used shorter chain PFAS replacement products may be problematic as it pertains to the accurate assessment of PFAS behaviour through drinking water treatment processes since only limited information is available for these PFASs.				●	●	●			-		C	-
402	環境中運命	Shi, Yali; Vestergren, Robin; Zhou, Zhen; Song, Xiaowei; Xu, Lin; Liang, Yong; Cai, Yaqi	Tissue distribution and whole body burden of the chlorinated polyfluoroalkyl ether sulfonic acid F-53B in crucian carp (Carassius carassius): Evidence for a highly bioaccumulative contaminant of emerging concern	2015	Environ Sci Technol. 2015 Dec 15;49(24):14156-65. doi: 10.1021/acs.est.5b04299. Epub 2015 Nov 24.	Following the global actions to phase out perfluorooctanesulfonic acid (PFOS) a large number of alternative per- and polyfluoroalkyl substances, with poorly defined hazard properties, are being used in increasing quantities. Here, we report on the first detection of the chlorinated polyfluoroalkyl ether sulfonic acid F-53B in biological samples and determine the tissue distribution and whole body bioaccumulation factors (BAFwhole body) in crucian carp (Carassius carassius). Analysis of fish samples from Xiaoqing River (XR) and Tangxun Lake (TL) demonstrated a similar level of F-53B contamination with median concentrations in blood of 41.9 and 20.9 ng/g, respectively. Tissue/blood ratios showed that distribution of F-53B primarily occurs to the kidney (TL: 0.48, XR: 0.54), gonad (TL: 0.36, XR: 0.54), liver (TL: 0.38, XR: 0.53), and heart (TL: 0.47, XR: 0.47). Median Log BAFwhole body values for F-53B (XR: 4.124, TL: 4.322) exceeded regulatory bioaccumulation criterion and were significantly higher than those of PFOS in the same data sets (XR: 3.430, TL: 3.279). On the basis of its apparent omnipresence and strong bioaccumulation propensity, it is hypothesized that F-53B could explain a significant fraction of previously unidentified organofluorine in biological samples from China, and regulatory actions for this compound are encouraged.				●					-		C	-
403	環境中運命	Shin, Hyeong-Moo; Vieira, Verónica M; Ryan, P Barry; Detwiler, Russell; Sanders, Brett; Steenland, Kyle; Bartell, Scott M	Environmental fate and transport modeling for perfluorooctanoic acid emitted from the Washington Works Facility in West Virginia	2011	Environ Sci Technol. 2011 Feb 15;45(4):1435-42. doi: 10.1021/es102769t. Epub 2011 Jan 12.	Perfluorooctanoic acid (PFOA) has been detected in environmental samples in Ohio and West Virginia near the Washington Works Plant in Parkersburg, West Virginia. This paper describes retrospective fate and transport modeling of PFOA concentrations in local air, surface water, groundwater, and six municipal water systems based on estimates of historic emission rates from the facility, physicochemical properties of PFOA, and local geologic and meteorological data beginning in 1951. We linked several environmental fate and transport modeling systems to model PFOA air dispersion, transit through the vadose zone, surface water transport, and groundwater flow and transport. These include AERMOD, PRZM-3, BreZo, MODFLOW, and MT3DMS. Several thousand PFOA measurements in municipal well water have been collected in this region since 1998. Our linked modeling system performs better than expected, predicting water concentrations within a factor of 2.1 of the average observed water concentration for each of the six municipal water districts after adjusting the organic carbon partition coefficient to fit the observed data. After model calibration, the Spearman's rank correlation coefficient for predicted versus observed water concentrations is 0.87. These models may be useful for estimating past and future public well water PFOA concentrations in this region.				●				●	-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報抽出対象	文献ランク①	文献ランク②
404	環境中運命	Simcik, Matt F	Aquatic processes and systems in perspective. Global transport and fate of perfluorochemicals	2005	J Environ Monit. 2005 Aug;7(8):759-63. doi: 10.1039/b509482h. Epub 2005 Jul 14.	No abstract available				●						アブストなし、要確認？		D	-
405	環境中運命	Small MJ.	Final report of the peer consultation panel conducting the review for the scientific peer consultation process for a site environmental assessment program as part of the Dupont-EPA memorandum of understanding and Phase II Workplan	2009	Pittsburgh, PA: Carnegie Mellon University, Civil and Environmental Engineering and Engineering and Public Policy.	No abstract available				●						企業データ		D	-
406	植物の取り込み	Stahl, Thorsten; Riebe, Rika Alessa; Falk, Sandy; Failing, Klaus; Brunn, Hubertus	Long-term lysimeter experiment to investigate the leaching of perfluoroalkyl substances (PFASs) and the carry-over from soil to plants: Results of a pilot study	2013	J Agric Food Chem. 2013 Feb 27;61(8):1784-93. doi: 10.1021/jf305003h. Epub 2013 Feb 18.	To study the behavior of perfluoroalkyl substances (PFASs) in soil and the carry-over from soil to plants, technical mixtures of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) at a concentration of 25 mg/kg soil were applied to 1.5 m(3) monolithic soil columns of a lysimeter. Growth samples and percolated water were analyzed for PFASs throughout a period of 5 years. In addition to PFOA/PFOS plant compartments and leachate were found to be contaminated with short-chain PFASs. Calculation showed significant decreasing trends (p < 0.05) for all substances tested in the growth samples. Short-chain PFASs and PFOA pass through the soil much more quickly than PFOS. Of the 360 g of PFOA and 367.5 g of PFOS applied to the soil, 96.88% PFOA and 99.98% PFOS were still present in the soil plot of the lysimeter after a period of 5 years. Plants accumulated 0.001% PFOA and 0.004% PFOS. Loss from the soil plot through leachate amounted to 3.12% for PFOA and 0.013% for PFOS.				●						-		B	-
407	環境中運命	Stasinakis, Athanasios S; Petalas, Anastasios V; Mamais, Daniel; Thomaidis, Nikolaos S	Application of the OECD 301F respirometric test for the biodegradability assessment of various potential endocrine disrupting chemicals	2008	Bioresour Technol. 2008 Jun;99(9):3458-67. doi: 10.1016/j.biortech.2007.08.002. Epub 2007 Sep 18.	The biodegradability of several potential endocrine disrupting compounds, namely 4-n-nonylphenol (4-n-NP), nonylphenol monoethoxylate (NP1EO), nonylphenol diethoxylate (NP2EO), bisphenol A (BPA), triclosan (TCS), di-(2-ethylhexyl)-phthalate (DEHP), perfluorooctanoate (PFOA) and perfluorononanoate (PFNA) was evaluated in this study, using OECD method 301F (manometric respirometry test) and activated sludge as inoculum. According to the results, 4-n-NP and BPA meet the strict definition of ready biodegradability and they are not expected to be persistent during the activated sludge process. Partial biodegradation was observed for DEHP (58.7+/-5.7%, n=3), TCS (52.1+/-8.5%, n=3) and NP1EO (25.9+/-8.1%, n=3), indicating their possible biodegradation in wastewater treatment systems, while no biodegradation was observed for NP2EO, PFOA and PFNA. Experiments in the co-presence of a readily biodegradable compound showed the absence of co-metabolic phenomena during 4-n-NP, BPA and TCS biodegradation. Using first order kinetics to describe biodegradation of the target compounds, half-lives of 4.3+/-0.6, 1.3+/-0.2, 1.8+/-0.5, 6.9+/-2.6 days were calculated for 4-n-NP, BPA, TCS and DEHP, respectively. Toxicity tests using marine bacterium Vibrio fischeri showed that biodegradation of 4-n-NP, NP1EO, BPA and TCS is a simultaneous detoxification process, while possible abiotic or biotic transformations of NP2EO, DEHP, PFOA and PFNA during respirometric test resulted to significant increase of their toxicities.				●						-		B	-
408	環境中運命	Washington, John W; Ellington, Jackson; Jenkins, Thomas M; Evans, John J; Yoo, Hoon; Hafner, Sarah C	Degradability of an acrylate-linked, fluorotelomer polymer in soil	2009	Environ Sci Technol. 2009 Sep 1;43(17):6617-23. doi: 10.1021/es9002668.	Fluorotelomer polymers are used in a broad array of products in modern societies worldwide and, if they degrade at significant rates, potentially are a significant source of perfluorooctanoic acid (PFOA) and related compounds to the environment To evaluate this possibility, we incubated an acrylate-linked fluorotelomer polymer in soil microcosms and monitored the microcosms for possible fluorotelomer (FT) and perfluorinated-compound (PFC) degradation products using GC/MS and LC/MS/MS. This polymer scavenged FTs and PFCs aggressively necessitating development of a multistep extraction using two solvents. Aged microcosms accumulated more FTs and PFCs than were present in the fresh polymer indicating polymer degradation with a half-life of about 870-1400 years for our coarse-grained test polymer. Modeling indicates that more-finely grained polymers in soils might have half-lives of about 10-17 years assuming degradation is surface-mediated. In our polymer-soil microcosms, PFOA evidently was lost with a half-life as short as 130 days, possibly by polymer-catalyzed degradation. These results suggest that fluoratelomer-polymer degradation is a significant source of PFOA and other fluorinated compounds to the environment.				●						-		B	-
409	環境中運命	Washington, John W; Jenkins, Thomas M	Abiotic hydrolysis of fluorotelomer-based polymers as a source of perfluorocarboxylates at the global scale	2015	Environ Sci Technol. 2015 Dec 15;49(24):14129-35. doi: 10.1021/acs.est.5b03686. Epub 2015 Nov 24.	Fluorotelomer-based polymers (FTPs) are the main product of the fluorotelomer industry. For nearly 10 years, whether FTPs degrade to form perfluorooctanoate (PFOA) and perfluorocarboxylate (PFCA) homologues has been vigorously contested. Here we show that circum-neutral abiotic hydrolysis of a commercial FTP proceeds with half-life estimates of 55-89 years and that base-mediated hydrolysis overtakes neutral hydrolysis at about pH = 10, with a half-life of ~0.7 years at pH ~ 12. Considered in light of the large production volume of FTPs and the poor efficacy of conventional treatments for recovery of PFCAs from waste streams, these results suggest that FTPs manufactured to date potentially could increase PFCAs 4- to 8-fold over current oceanic loads, largely depending on the integrity of disposal units to contain PFCAs upon hydrolytic generation from FTPs.				●					●	-		B	-
410	環境中運命	Washington, John W; Jenkins, Thomas M; Rankin, Keegan; Naile, Jonathan E	Decades-scale degradation of commercial, side-chain, fluorotelomer-based polymers in soils and water	2015	Environ Sci Technol. 2015 Jan 20;49(2):915-23. doi: 10.1021/es504347u.	Fluorotelomer-based polymers (FTPs) are the primary product of the fluorotelomer industry. Here we report on a 376-day study of the degradability of two commercial acrylate-linked FTPs in four saturated soils and in water. Using an exhaustive serial extraction, we report GC/MS and LC/MS/MS results for 50 species including fluorotelomer alcohols and acids, and perfluorocarboxylates. Modeling of seven sampling rounds, each consisting of ≥5 replicate microcosm treatments, for one commercial FTP in one soil yielded half-life estimates of 65–112 years and, when the other commercial FTP and soils were evaluated, the estimated half-lives ranged from 33 to 112 years. Experimental controls, consisting of commercial FTP in water, degraded roughly at the same rate as in soil. A follow-up experiment, with commercial FTP in pH 10 water, degraded roughly 10-fold faster than the circum-neutral control suggesting that commercial FTPs can undergo OH−-mediated hydrolysis. 8:2Fluorotelomer alcohol generated from FTP degradation in soil was more stable than without FTP present suggesting a clathrate guest–host association with the FTP. To our knowledge, these are the only degradability-test results for commercial FTPs that have been generated using exhaustive extraction procedures. They unambiguously show that commercial FTPs, the primary product of the fluorotelomer industry, are a source of fluorotelomer and perfluorinated compounds to the environment.				●					●	-		B	-
411	環境中運命	Yarwood, Greg; Kemball-Cook, Susan; Keinath, Michael; Waterland, Robert L; Korzeniowski, Stephen H; Buck, Robert C; Russell, Mark H; Washburn, Stephen T	High-resolution atmospheric modeling of fluorotelomer alcohols and perfluorocarboxylic acids in the North American troposphere	2007	Environ Sci Technol. 2007 Aug 15;41(16):5756-62. doi: 10.1021/es0708971.	A high spatial and temporal resolution atmospheric model is used to evaluate the potential contribution of fluorotelomer alcohol (FTOH) and perfluorocarboxylate (PFCA) emissions associated with the manufacture, use, and disposal of DuPont fluorotelomer-based products in North America to air concentrations of FTOH, perfluorooctanoic acid (PFOA), and perfluorononanoic acid (PFNA) in North America and the Canadian Arctic. A bottom-up emission inventory for PFCAs and FTOHs was developed from sales and product composition data. A detailed FTOH atmospheric degradation mechanism was developed to simulate FTOH degradation to PFCAs and model atmospheric transport of PFCAs and FTOHs. Modeled PFCA yields from FTOH degradation agree with experimental smog-chamber results supporting the degradation mechanism used. Estimated PFCA and FTOH air concentrations and PFCA deposition fluxes are compared to monitoring data and previous global modeling. Predicted FTOH air concentrations are generally in agreement with available monitoring data. Overall emissions from the global fluorotelomer industry are estimated to contribute approximately 1-2% of the PFCAs in North American rainfall, consistent with previous global emissions estimates. Emission calculations and modeling results indicate that atmospheric inputs of PFCAs in North America from fluorotelomer-based products will decline by an order of magnitude in the near future as a result of current industry commitments to reduce manufacturing emissions and lower the residual fluorotelomer alcohol raw material and trace PFCA product content.				●						-		B	-
412	環境中運命	Yeung, Leo W Y; Dassuncao, Clifton; Mabury, Scott; Sunderland, Elsie M; Zhang, Xianming; Lohmann, Rainer	Vertical profiles, sources, and transport of PFASs in the Arctic Ocean	2017	Environ Sci Technol. 2017 Jun 20;51(12):6735-6744. doi: 10.1021/acs.est.7b00788. Epub 2017 Jun 5.	The relative importance of atmospheric versus oceanic transport for poly- and perfluorinated alkyl substances (PFASs) reaching the Arctic Ocean is not well understood. Vertical profiles from the Central Arctic Ocean and shelf water, snow and meltwater samples were collected in 2012; 13 PFASs (C6-C12 PFCAs; C6, 8, 10 PFSAs; MeFOSAA and EtFOSAA; and FOSA) were routinely detected (range: <5-343 pg/L). PFASs were only detectable above 150 m depth in the polar mixed layer (PML) and halocline. Enhanced concentrations were observed in snow and meltpond samples, implying atmospheric deposition as an important source of PFASs. Model results suggested atmospheric inputs to account for 34-59% (~11-19 pg/L) of measured PFOA concentrations in the PML (mean 32 ± 15 pg/L). Modeled surface and halocline measurements for PFOS based on North Atlantic inflow (11-36 pg/L) agreed with measurements (mean, 17, range <5-41 pg/L). Modeled deep water concentrations below 200 m (5-15 pg/L) were slightly higher than measurements (<5 pg/L), suggesting the lower bound of PFAS emissions estimates from wastewater and rivers may provide the best estimate of inputs to the Arctic. Despite low concentrations in deep water, this reservoir is expected to contain most of the PFOS mass in the Arctic (63-180 Mg) and is projected to continue increasing to 2038.				●						-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報対象抽出	文献ランク①	文献ランク②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
413	環境中運命	Young, Cora J; Furdui, Vasile I; Franklin, James; Koerner, Roy M; Muir, Derek C G; Mabury, Scott A	Perfluorinated acids in Arctic snow: New evidence for atmospheric formation	2007	Environ Sci Technol. 2007 May 15;41(10):3455-61. doi: 10.1021/es0626234.	Perfluorinated acids (PFAs) are ubiquitously found in water and biota, including remote regions such as the High Arctic. Under environmental conditions, PFAs exist mainly as anions and are not expected to be subject to long-range atmospheric transport in the gas phase. Fluorinated telomer alcohols (FTOHs) are volatile and can be atmospherically oxidized to form perfluorocarboxylic acids. Analogously, fluorosulfamido alcohols can be oxidized to form perfluorooctane sulfonate (PFOS). High Arctic ice caps experience contamination solely from atmospheric sources. By examining concentrations of PFAs in ice cap samples, it is possible to determine atmospheric fluxes to the Arctic. Ice samples were collected from high Arctic ice caps in the spring of 2005 and 2006. Samples were concentrated using solid-phase extraction and analyzed by LC-MS-MS. PFAs were observed in all samples, dating from 1996 to 2005. Concentrations were in the low-mid pg L(-1) range and exhibited seasonality, with maximum concentrations in the spring-summer. The presence of perfluorodecanoic acid (PFDA) and perfluoroundecanoic acid (PFUnA) on the ice cap was indicative of atmospheric oxidation as a source. Ratios of PFAs to sodium concentrations were highly variable, signifying PFA concentrations on the ice cap were unrelated to marine chemistry. Fluxes of the PFAs were estimated to the area north of 65 degrees N for the 2005 season, which ranged from 114 to 587 kg year(-1) for perfluorooctanoic acid (PFOA), 73 to 860 kg year(-1) for perfluorononanoic acid (PFNA), 16 to 84 kg year(-1) for PFDA, 26 to 62 kg year(-1) for PFUnA, and 18 to 48 kg year(-1) for PFOS. The PFOA and PFNA fluxes agreed with FTOH modeling estimations. A decrease in PFOS concentrations through time was observed, suggesting a fast response to changes in production. These data suggest that atmospheric oxidation of volatile precursors is a primary source of PFAs to the Arctic.				●						-		B	-
414	環境中運命	Zhao, Hongxia; Qu, Baocheng; Guan, Yue; Jiang, Jingqiu; Chen, Xiuying	Influence of salinity and temperature on uptake of perfluorinated carboxylic acids (PFCAs) by hydroponically grown wheat (Triticum aestivum L	2016	Springerplus. 2016 Apr 27;5:541. doi: 10.1186/s40064-016-2016-9. eCollection 2016.	Perfluoroalkyl substances (PFASs) have recently attracted increasing concerns due to their ubiquitous existence, adverse effects and persistence in environment. This study employed four perfluorinated carboxylic acids (PFCAs) to examine effects of salinity and temperature on the PFAS uptake in wheat, one of the major crops in the North China Plain. Wheat plants were grown in the spiked-PFCA hydroponic culture system at different salinities and temperatures. As expected, salinity and temperature significantly impacted the root uptake and translocation of wheat to four PFCAs, and the concentrations for each of PFCAs in wheat root and shoot increased with increasing salinity and temperature, respectively. PFCA concentrations at high salinity or high temperature were up to thrice those found at low salinity or low temperature. Except for perfluorobutanoic acid, the amount of PFCAs in root was always higher than that in shoot at the ranges of salinity and temperature tested. Additionally salinity and temperature were also capable of influencing the transfer factors (TFs) of four PFCAs, and significant increase was observed in the TFs in response to the increases in salinity and temperature.				●						-		B	-
415	環境中運命	Zareitalabad, P; Siemens, J; Hamer, M; Amelung, W.	Perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS) in surface waters, sediments, soils and wastewater - A review on concentrations and distribution coefficients [Review]	2013	Chemosphere 91: 725-732. doi: 10.1016/j.chemosphere.2013.02.024	The sorption of perfluorinated compounds (PFCs) to soils and sediments determines their fate and distribution in the environment, but there is little consensus regarding distribution coefficients that should be used for assessing the environmental fate of these compounds. Here we reviewed sorption coefficients for PFCs derived from laboratory experiments and compared these values with the gross distribution between the concentrations of PFCs in surface waters and sediments or between wastewater and sewage sludge. Sorption experiments with perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) suggest that their sorption can be described reasonably well as a partitioning-like process with an average log K(oc) of approximately 2.8 for PFOA and 3.0 for PFOS. However, median concentrations in sediments (PFOA, 0.27 ng g(-1); PFOS, 0.54 ng g(-1)) or sewage sludge (PFOA, 37 ng g(-1); PFOS, 69 ng g(-1)) in relation to median concentrations in surface water (PFOA, 3ngl(-1); PFOS, 3ngl(-1)) or wastewater treatment effluent (PFOA, 24 ng l(-1); PFOS, 11 ng l(-1)), suggest that effective log K(oc) distribution coefficients for the field situation may be close to 3.7 for PFOA and 4.2 for PFOS. Applying lab-based log K(oc) distribution coefficients can therefore result in a serious overestimation of PFC concentrations in water and in turn to an underestimation of the residence time of PFOA and PFOS in contaminated soils. Irrespective of the dissipation kinetics, the majority of PFOA and PFOS from contaminated soils will be transported to groundwater and surface water bodies.		●								-		B	-
416	蓄積性	Ge, H; Yamazaki, E; Yamashita, N; Taniyasu, S; Ogata, A; Furuuchi, M	Particle size specific distribution of perfluoro alkyl substances in atmospheric particulate matter in Asian cities	2017	Environ Sci Process Impacts. 2017 Apr 19;19(4):549-560. doi: 10.1039/c6em00564k.	Seasonal and local characteristics of perfluorinated alkylated substances (PFASs) were examined using size-segregated particles including an ultrafine range. The examination included sampling and analysis of ambient particles collected at four sites located in different environments in three different countries, Japan (Kanazawa and Okinawa), Hong Kong and India. To minimize the evaporation artefacts derived from PFASs during the sampling, an air sampler that permitted particles smaller than 0.1 μm (PM(0.1)) to be separated at a moderate pressure drop (<5-15 kPa), was used for all of the air sampling procedures. In the case of Kanazawa, a local city in Japan, the concentration of PFASs was found to be dominated by carboxylates, especially PFOA, PFNA and PFDA regardless of the particle size and sampling period. Ultrafine particles were found to be the largest contributor to the mass fraction of PFCAs, while the maximum PFOS mass fractions were determined to be in the coarse-sized fractions. The seasonal difference in the total PFAS concentration can be largely attributed to precipitation. The results were basically similar for all sites that were examined. The type of land use may be a more influencing factor on the mass fraction of the PFASs than the country of origin. The dependency of PFAS mass fraction on the specific surface of the particle suggests that ultrafine PFAS particles are segregated, not only by gas deposition but could also be segregated by a mechanism involving compositional dependence or the primary source of the particles. Other possible sources of PFASs, other than from traffic are also possible.									●	-	1	A	-
417	環境中運命	Joerss, H.; Xie, Z.; Wagner, C. C.; von Appen, W. J.; Sunderland, E. M.; Ebinghaus, R.	Transport of Legacy Perfluoroalkyl Substances and the Replacement Compound HFPO-DA through the Atlantic Gateway to the Arctic Ocean-Is the Arctic a Sink or a Source? Environ Sci Technol	2020	Environ Sci Technol. 2020 Aug 18;54(16):9958-9967. doi: 10.1021/acs.est.0c00228. Epub 2020 Jul 29.	The spatial distribution of 29 per- and polyfluoroalkyl substances (PFASs) in seawater was investigated along a sampling transect from Europe to the Arctic and two transects within Fram Strait, located between Greenland and Svalbard, in the summer of 2018 Hexafluoropropylene oxide-dimer acid (HFPO-DA), a replacement compound for perfluorooctanoic acid (PFOA), was detected in Arctic seawater for the first time. This provides evidence for its long-range transport to remote areas. The total PFAS concentration was significantly enriched in the cold, low-salinity surface water exiting the Arctic compared to warmer, higher-salinity water from the North Atlantic entering the Arctic (260 ± 20 pg/L versus 190 ± 10 pg/L). The higher ratio of perfluoroheptanoic acid (PFHpA) to perfluorononanoic acid (PFNA) in outflowing water from the Arctic suggests a higher contribution of atmospheric sources compared to ocean circulation. An east-west cross section of the Fram Strait, which included seven depth profiles, revealed higher PFAS concentrations in the surface water layer than in intermediate waters and a negligible intrusion into deep waters (>1000 m). Mass transport estimates indicated a net inflow of PFASs with ≥8 perfluorinated carbons via the boundary currents and a net outflow of shorter-chain homologues. We hypothesize that this reflects higher contributions from atmospheric sources to the Arctic outflow and a higher retention of the long-chain compounds in melting snow and ice.									●	-		B	-
418	環境中運命	Johansson, J H; Salter, M E; Acosta Navarro, J C; Leck, C; Nilsson, E D; Cousins, I T	Global transport of perfluoroalkyl acids via sea spray aerosol	2019	Environ Sci Process Impacts. 2019 Apr 17;21(4):635-649. doi: 10.1039/c8em00525g.	Perfluoroalkyl acids (PFAAs) are persistent organic pollutants found throughout the world's oceans. Previous research suggests that long-range atmospheric transport of these substances may be substantial. However, it remains unclear what the main sources of PFAAs to the atmosphere are. We have used a laboratory sea spray chamber to study water-to-air transfer of 11 PFAAs via sea spray aerosol (SSA). We observed significant enrichment of all PFAAs relative to sodium in the SSA generated. The highest enrichment was observed in aerosols with aerodynamic diameter < 1.6 μm, which had aerosol PFAA concentrations up to ∼62 000 times higher than the PFAA water concentrations in the chamber. In surface microlayer samples collected from the sea spray chamber, the enrichment of the substances investigated was orders of magnitude smaller than the enrichment observed in the aerosols. In experiments with mixtures of structural isomers, a lower contribution of branched PFAA isomers was observed in the surface microlayer compared to the bulk water. However, no clear trend was observed in the comparison of structural isomers in SSA and bulk water. Using the measured enrichment factors of perfluorooctanoic acid and perfluorooctane sulfonic acid versus sodium we have estimated global annual emissions of these substances to the atmosphere via SSA as well as their global annual deposition to land areas. Our experiments suggest that SSA may currently be an important source of these substances to the atmosphere and, over certain areas, to terrestrial environments.									●	-		B	-
419	環境中運命	Rankin, Keegan; Mabury, Scott A; Jenkins, Thomas M; Washington, John W	A North American and global survey of perfluoroalkyl substances in surface soils: Distribution patterns and mode of occurrence	2016	Chemosphere. 2016 Oct;161:333-341. doi: 10.1016/j.chemosphere.2016.06.109. Epub 2016 Jul 18.	The distribution of 32 per/polyfluoroalkyl substances (PFASs) in surface soils was determined at 62 locations representing all continents (North America n = 33, Europe n = 10, Asia n = 6, Africa n = 5, Australia n = 4, South America n = 3 and Antarctica n = 1) using ultra performance liquid chromatography tandem mass spectrometry (UPLC-MS/MS) systems. Quantifiable levels of perfluoroalkyl carboxylates (PFCAs: PFHxA-PFTeDA) were observed in all samples with total concentrations ranging from 29 to 14,300 pg/g (dry weight), while perfluoroalkane sulfonates (PFSAs: PFHxS, PFOS and PFDS) were detected in all samples but one, ranging from <LOQ-3270 pg/g, confirming the global distribution of PFASs in terrestrial settings. The geometric mean PFCA and PFSA concentrations were observed to be higher in the northern hemisphere (930 and 170 pg/g) compared to the southern hemisphere (190 and 33 pg/g). Perfluorooctanoate (PFOA) and perfluorooctanesulfonate (PFOS) were the most commonly detected analytes at concentrations up to 2670 and 3100 pg/g, respectively. The sum of PFCA homologues of PFOA commonly were roughly twice the concentration of PFOA. The PFCA and PFSA congener profiles were similar amongst most locations, with a few principal-component statistical anomalies suggesting impact from nearby urban and point sources. The ratio of even to odd PFCAs was consistent with the atmospheric oxidation of fluorotelomer-based precursors previously observed in laboratory and environmental studies. Given the soils were collected from locations absent of direct human activity, these results suggest that the atmospheric long-range transport (LRT) of neutral PFASs followed by oxidation and deposition are a significant source of PFCAs and PFSAs to soils.									●	-		C	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
420	環境中運命	Lai, Senchao; Song, Junwei; Song, Tianli; Huang, Zhijiong; Zhang, Yingyi; Zhao, Yan; Liu, Guicheng; Zheng, Junyu; Mi, Wenying; Tang, Jianhui; Zou, Shichun; Ebinghaus, Ralf; Xie, Zhiyong	Neutral polyfluoroalkyl substances in the atmosphere over the northern South China Sea	2016	Environ Pollut. 2016 Jul;214:449-455. doi: 10.1016/j.envpol.2016.04.047. Epub 2016 Apr 23.	Neutral Polyfluoroalkyl substances (PFASs) in the atmosphere were measured during a cruise campaign over the northern South China Sea (SCS) from September to October 2013. Four groups of PFASs, i.e., fluorotelomer alcohols (FTOHs), fluorotelomer acrylates (FTAs), fluorooctane sulfonamides (FOSAs) and fluorooctane sulfonamidoethanols (FASEs), were detected in gas samples. FTOHs was the predominant PFAS group, accounting for 95.2-99.3% of total PFASs (ΣPFASs), while the other PFASs accounted for a small fraction of ΣPFASs. The concentrations of ΣPFASs ranged from 18.0 to 109.9 pg m(-3) with an average of 54.5 pg m(-3). The concentrations are comparable to those reported in other marine atmosphere. Higher concentrations of ΣPFASs were observed in the continental-influenced samples than those in other samples, pointing to the substantial contribution of anthropogenic sources. Long-range transport is suggested to be a major pathway for introducing gaseous PFASs into the atmosphere over the northern SCS. In order to further understand the fate of gaseous PFASs during transport, the atmospheric decay of neutral PFASs under the influence of reaction with OH radicals and atmospheric physical processes were estimated. Concentrations of 8:2 FTOH, 6:2 FTOH and MeFBSE from selected source region to the atmosphere over the SCS after long-range transport were predicted and compared with the observed concentrations. It suggests that the reaction with OH radicals may play an important role in the atmospheric decay of PFAS during long-range transport, especially for shorted-lived species. Moreover, the influence of atmospheric physical processes on the decay of PFAS should be further considered.								●	-		C	-
421	蓄積性	de Vos, M. G.; Huijbregts, M. A.; van den Heuvel-Greve, M. J.; Vethaak, A. D.; Van de Vijver, K. I.; Leonards, P. E.; van Leeuwen, S. P.; de Voogt, P.; Hendriks, A. J.	Accumulation of perfluorooctane sulfonate (PFOS) in the food chain of the Western Scheldt estuary: Comparing field measurements with kinetic modeling	2008	Chemosphere. 2008 Feb;70(10):1766-73. doi: 10.1016/j.chemosphere.2007.08.038. Epub 2007 Oct 10.	The environmentally persistent perfluorooctane sulfonate (PFOS) is a perfluoroalkylated acid (PFA), which has been found to accumulate and biomagnify through food webs all over the world. In the present investigation, the accumulation kinetics of PFOS was explored using the bioaccumulation model OMEGA. As accumulation behavior of PFOS may show similarities to fatty acids as well as to neutral organic compounds, different modeling approaches were used. Accumulation kinetics of PFOS was modeled similar to -1 moderately and -2 highly hydrophobic compounds, -3 metals and -4 as a combination of hydrophobic compounds and metals. Modeled elimination and uptake rate constants were compared to empirical rate constants from literature. Subsequently, model predictions were compared to field-based biota-suspended solids accumulation ratios (BSAF) in the estuarine food chain of the Western Scheldt, The Netherlands. Results show that uptake of PFOS is comparable to moderately hydrophobic compounds and elimination is best described by elimination kinetics of metals. These observations indicate that the accumulation behavior of PFOS is comparable to that of short and medium chained fatty acids.	●	●		●						-		B	-
422	蓄積性	Fang, S.; Chen, X.; Zhao, S.; Zhang, Y.; Jiang, W.; Yang, L.; Zhu, L.	Trophic magnification and isomer fractionation of perfluoroalkyl substances in the food web of Taihu Lake, China	2014	Environ Sci Technol. 2014 Feb 18;48(4):2173-82. doi: 10.1021/es405018b. Epub 2014 Feb 6.	Biomagnification of perfluoroalkyl substances (PFASs) are well studied in marine food webs, but related information in fresh water ecosystem and knowledge on fractionation of their isomers along the food web are limited. The distribution, bioaccumulation, magnification, and isomer fractionation of PFASs were investigated in a food web of Taihu Lake, China. Perfluorooctanesulfonate (PFOS) and perfluorocarboxylates (PFCAs) with longer carbon chain lengths, such as perfluorodecanoate (PFDA) and perfluoroundecanoate (PFUnA), were predominant in organisms, while perfluorohexanoate (PFHxA) and perfluorooctanoate (∑PFOA) contributed more in the water phase. The consistent profile signature of PFOA isomers in water phase with 3M electrochemical fluorination (ECF) products suggests that ECF production of PFOA still exists in China. Linear proportions of PFOA, PFOS and perfluorooctane sulfonamide (PFOSA) in the biota were in the range of 91.9-100%, 78.6-95.5%, and 72.2-95.5%, respectively, indicating preferential bioaccumulation of linear isomers in biota. Trophic magnification factors (TMFs) were estimated for PFDA (2.43), perfluorododecanoate (PFDoA) -2.68 and PFOS -3.46 when all biota were included, suggesting that PFOS and long-chained PFCAs are biomagnified in the fresh water food web. The TMF of PFOS isomers descended in the order: n-PFOS -3.86 > 3+5m-PFOS -3.35 > 4m-PFOS -3.32 > 1m-PFOS -2.92 > m2-PFOS -2.67 > iso-PFOS (2.59), which is roughly identical to their elution order on a FluoroSep-RP Octyl column, suggesting that hydrophobicity may be an important contributor for isomer discrimination in biota.	●	●								-		B	-
423	蓄積性	Haukås, M.; Berger, U.; Hop, H.; Gulliksen, B.; Gabrielsen, G. W.	Bioaccumulation of per- and polyfluorinated alkyl substances (PFAS) in selected species from the Barents Sea food web	2007	Environ Pollut. 2007 Jul;148(1):360-71. doi: 10.1016/j.envpol.2006.09.021. Epub 2007 Jan 25.	The present study reports concentrations and biomagnification potential of per- and polyfluorinated alkyl substances (PFAS) in species from the Barents Sea food web. The examined species included sea ice amphipod (Gammarus wilkitzkii), polar cod (Boreogadus saida), black guillemot (Cepphus grylle) and glaucous gull (Larus hyperboreus). These were analyzed for PFAS, polychlorinated biphenyls (PCBs), dichlorodiphenyltrichloroethanes (DDTs) and polybrominated diphenyl ethers (PBDEs). Perfluorooctane sulfonate (PFOS) was the predominant of the detected PFAS. Trophic levels and food web transfer of PFAS were determined using stable nitrogen isotopes (delta(15)N). No correlation was found between PFOS concentrations and trophic level within species. However, a non-linear relationship was established when the entire food web was analyzed. Biomagnification factors displayed values >1 for perfluorohexane sulfonate (PFHxS), perfluorononanoic acid (PFNA), PFOS and SigmaPFAS(7). Multivariate analyses showed that the degree of trophic transfer of PFAS is similar to that of PCB, DDT and PBDE, despite their accumulation through different pathways.	●	●								-		B	-
424	蓄積性	Houde, Magali; Martin, Jonathan W; Letcher, Robert J; Solomon, Keith R; Muir, Derek C G	Biological Monitoring of Polyfluoroalkyl Substances: A Review [Review]	2006	Environ Sci Technol. 2006 Jun 1;40(11):3463-73. doi: 10.1021/es052580b.	Polyfluoroalkyl substances (PFSs) are used in industrial and commercial products and can degrade to persistent perfluorocarboxylates (PFCAs) and perfluoroalkyl sulfonates (PFSAs). Temporal trend studies using human, fish, bird, and marine mammal samples indicate that exposure to PFSs has increased significantly over the past 15-25 years. This review summarizes the biological monitoring of PFCAs, PFSAs, and related PFSs in wildlife and humans, compares concentrations and contamination profiles among species and locations, evaluatesthe bioaccumulation/biomagnification in the environment, discusses possible sources, and identifies knowledge gaps. PFSs can reach elevated concentrations in humans and wildlife inhabiting industrialized areas of North America, Europe, and Asia (2-30,000 ng/ mL or ng/g of wet weight (ww)). PFSs have also been detected in organisms from the Arctic and mid-ocean islands (< or = 3000 ng/g ww). In humans, PFSAs and PFCAs have been shown to vary among ethnic groups and PFCA/PFSA profiles differ from those in wildlife with high proportions of perfluorooctanoic acid and perfluorooctane sulfonate. The pattern of contamination in wildlife varied among species and locations suggesting multiple emission sources. Food web analyses have shown that PFCAs and PFSAs can bioaccumulate and biomagnify in marine and freshwater ecosystems. Knowledge gaps with respect to the transport, accumulation, biodegradation, temporal/spatial trends and PFS precursors have been identified. Continuous monitoring with key sentinel species and standardization of analytical methods are recommended.	●	●	●	●					●	-		B	-
425	蓄積性	Kannan, Kurunthachalam; Tao, Lin; Sinclair, Ewan; Pastva, Stephanie D; Jude, Dave J; Giesy, John P	Perfluorinated compounds in aquatic organisms at various trophic levels in a Great Lakes food chain	2005	Arch Environ Contam Toxicol. 2005 May;48(4):559-66. doi: 10.1007/s00244-004-0133-x.	Trophic transfer of perfluorooctanesulfonate (PFOS) and other related perfluorinated compounds was examined in a Great Lakes benthic foodweb including water-algae-zebra mussel-round goby-smallmouth bass. In addition, perfluorinated compounds were measured in livers and eggs of Chinook salmon and lake whitefish, in muscle tissue of carp, and in eggs of brown trout collected from Michigan. Similarly, green frog livers, snapping turtle plasma, mink livers, and bald eagle tissues were analyzed to determine concentrations in higher trophic-level organisms in the food chain. PFOS was the most widely detected compound in benthic organisms at various trophic levels. Concentrations of PFOS in benthic invertebrates such as amphipods and zebra mussels were approximately 1000-fold greater than those in surrounding water, which suggested a bioconcentration factor (BCF; concentration in biota/concentration in water) of 1000 in benthic invertebrates. Concentrations of PFOS in round gobies were two- to fourfold greater than those in their prey organisms such as zebra mussels and amphipods. Concentrations of PFOS in predatory fishes (Chinook salmon and lake whitefish) were 10 to 20-fold greater than those in their prey species. Concentrations of PFOS in mink and bald eagles were, on average, 5- to 10-fold greater than those in Chinook salmon, carp, or snapping turtles. Because of the accumulation of PFOS in liver and blood, the biomagnification factor (BMF) of perfluorinated compounds in higher trophic-level organisms such as salmonid fishes, mink, and eagles were based on the concentrations in livers or plasma. Overall, these results suggest a BCF of PFOS of approximately 1000 (whole-body based) in benthic invertebrates, and a BMF of 10 to 20 in mink or bald eagles, relative to their prey items. Eggs of fish contained notable concentrations of PFOS, suggesting oviparous transfer of this compound. PFOA was found in water, but its biomagnification potential was lower than that of PFOS.	●	●		●						-		B	-
426	蓄積性	Kelly, Barry C; Ikonomou, Michael G; Blair, Joel D; Surridge, Blair; Hoover, Dale; Grace, Richard; Gobas, Frank A P C	Perfluoroalkyl contaminants in an Arctic marine food web: trophic magnification and wildlife exposure	2009	Environ Sci Technol. 2009 Jun 1;43(11):4037-43. doi: 10.1021/es9003894.	To better understand the bioaccumulation behavior of perfluoroalkyl contaminants (PFCs), we conducted a comparative analysis of PFCs and lipophilic organohalogens in a Canadian Arctic marine food web. Concentrations of perfluorooctane sulfonic acid (PFOS), perfluorooctansulfoamide (PFOSA), and C7-C14 perfluorocarboxylic acids (PFCAs) ranged between 0.01 and 0.1 ng x g(-1) dry wt in sediments and 0.1 and 40 ng x g(-1) wet wt in biota, which was equivalent to or higher than levels of PCBs, PBDEs, and organochlorine pesticides. In beluga whales, PFOS and PFCA concentrations were higher (P < 0.05) in protein-rich compartments (liver and blood), compared to other tissues/fluids (milk, blubber, muscle, and fetus). In the marine mammalian food web, concentrations of PFOSA and lipophilic organochlorines (ng x g(-1) lipid equivalent) and proteinophilic substances (i.e., PFOS and C8-C14 PFCAs, ng x g(-1) protein) increased significantly (P < 0.05) with trophic level. Trophic magnification factors (TMFs) of organochlorines ranged between 5 and 14 and exhibited significant curvilinear relationships (P < 0.05) with octanol-water and octanol-air partition coefficients (KOW, KOA). TMFs of perfluorinated acids (PFAs) ranged between 2 and 11 and exhibited similar correlation (P < 0.05) with protein-water and protein-air partition coefficients (KPW, KPA). PFAs did not biomagnify in the aquatic piscivorous food web (TMF range: 0.3-2). This food web specific biomagnification behavior was attributed to the high aqueous solubility and low volatility of PFAs. Specifically, the anticipated phase-partitioning of these proteinophilic substances, represented by their protein-water (KPW) and protein-air (KPA) partition coefficients, likely results in efficient respiratory elimination in water-respiring organisms but very slow elimination and biomagnification in air-breathing animals. Lastly, the results indicate that PFOS exposure in nursing Hudson Bay beluga whale calves (CI95 range = 2.7 x 10(-5) to 1.8 x 10(-4) mg x kg bw(-1) x d(-1)), exceedsthe oral reference dose for PFOS (7.5 x 10(-5) mg x kg bw(-1) x d(-1)), which raises concern for potential biological effects in these and other sensitive Arctic marine wildlife species.	●	●	●							-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
427	蓄積性	Loi, Eva I H; Yeung, Leo W Y; Taniyasu, Sachi; Lam, Paul K S; Kannan, Kurunthachalam; Yamashita, Nobuyoshi	Trophic Magnification of Poly- and Perfluorinated Compounds in a Subtropical Food Web	2011	Environ Sci Technol. 2011 Jul 1;45(13):5506-13. doi: 10.1021/es200432n. Epub 2011 Jun 6.	Perfluorinated compounds (PFCs) are known to biomagnify in temperate and Arctic food webs, but little is known about their behavior in subtropical systems. The environmental distribution and biomagnification of PFCs, extractable organic fluorine (EOF), and total fluorine were investigated in a subtropical food web. Surface water, sediment, phytoplankton, zooplankton, gastropods, worms, shrimps, fishes, and waterbirds collected in the Mai Po Marshes Nature Reserve in Hong Kong were analyzed. Trophic magnification was observed for perfluorooctanesulfonate (PFOS), perfluorodecanoate (PFDA), perfluoroundecanoate (PFUnDA), and perfluorododecanoate (PFDoDA) in this food web. Risk assessment results for PFOS, PFDA, and perfluorooctanoate (PFOA) suggest that current PFC concentrations in waterbird livers are unlikely to pose adverse biological effects to waterbirds. All hazard ratio (HR) values reported for PFOS and PFOA are less than one, which suggests that the detected levels will not cause any immediate health effects to the Hong Kong population through the consumption of shrimps and fishes. However, only 10-12% of the EOF in the shrimp samples was comprised of known PFCs, indicating the need for further investigation to identify unknown fluorinated compounds in wildlife.	●	●		●						-		B	-
428	蓄積性	Ng, Carla A; Hungerbühler, Konrad	Bioaccumulation of perfluorinated alkyl acids: Observations and models [Review]	2014	Environ Sci Technol. 2014 May 6;48(9):4637-48. doi: 10.1021/es404008g. Epub 2014 Apr 25.	In this review, we consider the two prevailing hypotheses for the mechanisms that control the bioaccumulation of perfluorinated alkyl acids (PFAAs). The first assumes that partitioning to membrane phospholipids, which have a higher affinity for charged species than neutral storage lipids, can explain the high bioaccumulation potential of these compounds. The second assumes that interactions with proteins--including serum albumin, liver fatty acid binding proteins (L-FABP), and organic anion transporters--determine the distribution, accumulation and half-lives of PFAAs. We consider three unique phenomena to evaluate the two models: (1) observed patterns of tissue distribution in the laboratory and field, (2) the relationship between perfluorinated chain length and bioaccumulation, and (3) species- and gender-specific variation in elimination half-lives. Through investigation of these three characteristics of PFAA bioaccumulation, we show the strengths and weaknesses of the two modeling approaches. We conclude that the models need not be mutually exclusive, but that protein interactions are needed to explain some important features of PFAA bioaccumulation. Although open questions remain, further research should include perfluorinated alkyl substances (PFASs) beyond the long-chain PFAAs, as these substances are being phased out and replaced by a wide variety of PFASs with largely unknown properties and bioaccumulation behavior.	●	●	●							-		B	-
429	蓄積性	Penland, T. N.; Cope, W. G.; Kwak, T. J.; Strynar, M. J.; Grieshaber, C. A.; Heise, R. J.; Sessions, F. W.	Trophodynamics of Per- and Polyfluoroalkyl Substances in the Food Web of a Large Atlantic Slope River	2020	Environ Sci Technol. 2020 Jun 2;54(11):6800-6811. doi: 10.1021/acs.est.9b05007. Epub 2020 May 12.	Per- and polyfluoroalkyl substances (PFASs) have attracted scientific and regulatory attention due to their persistence, bioaccumulative potential, toxicity, and global distribution. We determined the accumulation and trophic transfer of 14 PFASs within the food web of the Yadkin-Pee Dee River of North Carolina and South Carolina, USA. Food web components and pathways were determined by stable isotope analyses of producers, consumers, and organic matter. Analyses of water, sediment, organic matter, and aquatic biota revealed that PFASs were prevalent in all food web compartments, with most detections and greatest concentrations in aquatic insects. All 14 PFASs were detected in individual aquatic insect samples (range, < limit of detection [<LOD] - 1670 ng/g wet weight [WW]) and individual fish tissue samples (range, <LOD - 797 ng/g WW). Perfluorooctane sulfonate (PFOS) was the dominant PFAS among all samples (64%). The ova of an imperiled fish, the Robust Redhorse (Moxostoma robustum), had concentrations of 10 PFASs (range, <LOD - 483 ng/g WW) and PFOS concentration was exceptionally high (483 ng/g WW), indicating likely maternal transfer. Our findings demonstrate the prevalence of PFASs in a freshwater food web with potential implications for ecological and human health.	●	●								-		B	-
430	蓄積性	Pérez, F.; Nadal, M.; Navarro-Ortega, A.; Fàbrega, F.; Domingo, J. L.; Barceló, D.; Farré, M.	Accumulation of perfluoroalkyl substances in human tissues	2013	Environ Int. 2013 Sep;59:354-62. doi: 10.1016/j.envint.2013.06.004. Epub 2013 Jul 25.	Perfluoroalkyl substances (PFASs) are environmental pollutants with an important bioaccumulation potential. However, their metabolism and distribution in humans are not well studied. In this study, the concentrations of 21 PFASs were analyzed in 99 samples of autopsy tissues (brain, liver, lung, bone, and kidney) from subjects who had been living in Tarragona (Catalonia, Spain). The samples were analyzed by solvent extraction and online purification by turbulent flow and liquid chromatography coupled to tandem mass spectrometry. The occurrence of PFASs was confirmed in all human tissues. Although PFASs accumulation followed particular trends depending on the specific tissue, some similarities were found. In kidney and lung, perfluorobutanoic acid was the most frequent compound, and at highest concentrations (median values: 263 and 807ng/g in kidney and lung, respectively). In liver and brain, perfluorohexanoic acid showed the maximum levels (median: 68.3 and 141ng/g, respectively), while perfluorooctanoic acid was the most contributively in bone (median: 20.9ng/g). Lung tissues accumulated the highest concentration of PFASs. However, perfluorooctane sulfonic acid and perfluorooctanoic acid were more prevalent in liver and bone, respectively. To the best of our knowledge, the accumulation of different PFASs in samples of various human tissues from the same subjects is here reported for the very first time. The current results may be of high importance for the validation of physiologically based pharmacokinetic models, which are being developed for humans. However, further studies on the distribution of the same compounds in the human body are still required.	●	●	●	●						-		B	-
431	蓄積性	Powley, C. R.; George, S. W.; Russell, M. H.; Hoke, R. A.; Buck, R. C.	Polyfluorinated chemicals in a spatially and temporally integrated food web in the Western Arctic	2008	Chemosphere. 2008 Jan;70(4):664-72. doi: 10.1016/j.chemosphere.2007.06.067. Epub 2007 Aug 14.	This study reports on an investigation of the presence of polyfluorinated chemicals in a spatially and temporally integrated set of biological samples representing an Arctic food web. Zooplankton, Arctic cod, and seal tissues from the western Canadian Arctic were analyzed for perfluoroalkyl sulfonates [PFAS], perfluorocarboxylates [PFCAs], and other polyfluorinated acids. Perfluorooctane sulfonate [PFOS] was found in all samples [0.20-34 ng/g] and in the highest concentrations. PFCAs from nine to 12 carbons were quantified in most of the samples [0.28-6.9 ng/g]. PFCAs with carbon chain lengths of eight or less were not detected. Likewise, 44775 fluorotelomer acid [8-2 FTA] and 44775 fluorotelomer unsaturated acid [8-2 FTUA], products of fluorotelomer environmental transformation, were not detected. 2H,2H,3H,3H, heptadecafluoro decanoic acid [7-3 Acid], an additional metabolite from fluorotelomer biological transformation, was detected only in seal liver tissue [0.5-2.5 ng/g]. The ratios of branched to linear PFOS isomers in fish and seal tissue were not similar and did not match that of technical PFOS as manufactured. No branched PFCA isomers were detected in any samples. It is concluded that differing pharmacokinetics complicate the use of branched to linear ratios of PFCAs in attributing their presence to a specific manufacturing process. A statistical analysis of the data revealed significant correlations between PFOS and the PFCAs detected as well as among the PFCAs themselves. The 44745 Acid was not correlated with either PFCAs or PFAS, which suggests that it may have a different exposure pathway.	●	●		●						-		B	-
432	蓄積性	Ruffle, Betsy; Vedagiri, Usha; Bogdan, Dorin; Maier, Martha; Schwach, Catherine; Murphy-Hagan, Clare	Perfluoroalkyl Substances in U	2020	Environ Res. 2020 Nov;190:109932. doi: 10.1016/j.envres.2020.109932. Epub 2020 Jul 25.	Over the past two decades the class of per- and polyfluoroalkyl substances (PFAS) has emerged as a widespread contaminant in environmental media globally. As awareness and understanding of its prevalence, persistence, and potential health risks grows, so have concerns about human exposure. While drinking water has received substantial attention, dietary intakes have also been reported to contribute significantly to total exposure, with fish consumption in particular. Most studies of U.S. fish have targeted sport fish from areas of known or suspected contamination. This study was undertaken to improve data on PFAS levels in the U.S. commercial seafood supply. A total of 70 samples of finfish and shellfish were purchased at U.S. grocery stores and fish markets and analyzed for 26 PFAS compounds. The samples included a range of marine and freshwater species from four regions of the U.S. and seven countries with significant imports to the U.S. Up to ten PFAS were detected in 21 samples, with PFOS the predominant compound. There were no detections in the remaining 49 samples (detection limits of approximately 0.4-0.5 ppb). Total PFAS concentrations in most samples were single digit or sub-ppb levels. The exception was commercial finfish from the Great Lakes area, for which higher levels (up to 22 ppb) were observed in whitefish, walleye, and yellow perch fillet. Study findings suggest PFAS is present at low or non-detect levels in the U.S. commercial seafood supply and exposure is low for consumers of market basket fish and shellfish.	●	●								-		B	-
433	蓄積性	Tomy, G. T.; Budakowski, W.; Halldorson, T.; Helm, P. A.; Stern, G. A.; Friesen, K.; Pepper, K.; Tittlemier, S. A.; Fisk, A. T.	Fluorinated organic compounds in an eastern Arctic marine food web	2004	Environ Sci Technol. 2004 Dec 15;38(24):6475-81. doi: 10.1021/es049620g.	An eastern Arctic marine food web was analyzed for perfluorooctanesulfonate (PFOS, C8F17SO3-), perfluorooctanoate (PFOA, C7F15COO-), perfluorooctane sulfonamide (PFOSA, C8F17SO2NH2), and N-ethylperfluorooctane sulfonamide (N-EtPFOSA, C8F17SO2NHCH2CH3) to examine the extent of bioaccumulation. PFOS was detected in all species analyzed, and mean concentrations ranged from 0.28 +/- 0.09 ng/g (arithmetic mean +/- 1 standard error, wet wt, whole body) in clams (Mya truncata) to 20.2 +/- 3.9 ng/g (wet wt, liver) in glaucous gulls (Larus hyperboreus). PFOA was detected in approximately 0.4 of the samples analyzed at concentrations generally smaller than those found for PFOS; the greatest concentrations were observed in zooplankton (2.6 +/- 0.3 ng/g, wet wt). N-EtPFOSA was detected in all species except redfish with mean concentrations ranging from 0.39 +/- 0.07 ng/g (wet wt) in mixed zooplankton to 92.8 +/- 41.9 ng/g (wet wt) in Arctic cod (Boreogadus saida). This is the first report of N-EtPFOSA in Arctic biota. PFOSA was only detected in livers of beluga (Delphinapterus leucas) (20.9 +/- 7.9 ng/g, wet wt) and narwhal (Monodon monoceros) (6.2 +/- 2.3 ng/g, wet wt), suggesting that N-EtPFOSA and other PFOSA-type precursors are likely present but are being biotransformed to PFOSA. A positive linear relationship was found between PFOS concentrations (wet wt) and trophic level (TL), based on delta15N values, (r2 = 0.51, p < 0.0001) resulting in a trophic magnification factor of 3.1. TL-corrected biomagnification factor estimates for PFOS ranged from 0.4 to 9 Both results indicate that PFOS biomagnifies in the Arctic marine food web when liver concentrations of PFOS are used for seabirds and marine mammals. However, transformation of N-EtPFOSA and PFOSA and potential other perfluorinated compounds to PFOS may contribute to PFOS levels in marine mammals and may inflate estimated biomagnification values. None of the other fluorinated compounds (N-EtPFOSA, PFOSA, and PFOA) were found to have a significant relationship with TL, but BMF(TL) values of these compounds were often >1, suggesting potential for these compounds to biomagnify. The presence of perfluorinated compounds in seabirds and mammals provides evidence that trophic transfer is an important exposure route of these chemicals to Arctic biota.	●	●		●						-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ラン①抽出	文献ラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
434	蓄積性	Xu, J.; Guo, C. S.; Zhang, Y.; Meng, W.	Bioaccumulation and trophic transfer of perfluorinated compounds in a eutrophic freshwater food web	2014	Environ Pollut. 2014 Jan;184:254-61. doi: 10.1016/j.envpol.2013.09.011. Epub 2013 Sep 25.	In this study, the bioaccumulation of perfluorinated compounds from a food web in Taihu Lake in China was investigated. The organisms included egret bird species, carnivorous fish, omnivorous fish, herbivorous fish, zooplankton, phytoplankton, zoobenthos and white shrimp. Isotope analysis by δ(13)C and δ(15)N indicated that the carnivorous fish and egret were the top predators in the studied web, occupying trophic levels intermediate between 3.66 and 4.61, while plankton was at the lowest trophic level. Perfluorinated carboxylates (PFCAs) with 44816 carbons were significantly biomagnified, with trophic magnification factors (TMFs) ranging from 2.1 to 3.7. The TMF of perfluorooctane sulfonate (PFOS) -2.9 was generally comparable to or lower than those of the PFCAs in the same food web. All hazard ratio (HR) values reported for PFOS and perfluorooctanoate (PFOA) were less than unity, suggesting that the detected levels would not cause any immediate health effects to the people in Taihu Lake region through the consumption of shrimps and fish.	●	●							-		B	-
435	蓄積性	Felizeter, Sebastian; McLachlan, Michael S; de Voogt, Pim	Uptake of perfluorinated alkyl acids by hydroponically grown lettuce (Lactuca sativa)	2012	Environ Sci Technol. 2012 Nov 6;46(21):11735-43. doi: 10.1021/es302398u. Epub 2012 Oct 18.	An uptake study was carried out to assess the potential human exposure to perfluorinated alkyl acids (PFAAs) through the ingestion of vegetables. Lettuce (Lactuca sativa) was grown in PFAA-spiked nutrient solutions at four different concentrations, ranging from 10 ng/L to 10 μg/L. Eleven perfluorinated carboxylic acids (PFCAs) and three perfluorinated sulfonic acids (PFSAs) were analyzed by HPLC-MS/MS. At the end of the experiment, the major part of the total mass of each of the PFAAs (except the short-chain, C4-C7, PFCAs) taken up by plants appeared to be retained in the nonedible part, viz. the roots. Root concentration factors (RCF), foliage/root concentration factors (FRCF), and transpiration stream concentration factors (TSCF) were calculated. For the long chained PFAAs, RCF values were highest, whereas FRCF were lowest. This indicates that uptake by roots is likely governed by sorption of PFAAs to lipid-rich root solids. Translocation from roots to shoots is restricted and highly depending on the hydrophobicity of the compounds. Although the TSCF show that longer-chain PFCAs (e.g., perfluorododecanoic acid) get better transferred from the nutrient solution to the foliage than shorter-chain PFCAs (e.g., perfluoroheptanoic acid), the major fraction of longer-chain PFCAs is found in roots due to additional adsorption from the spiked solution. Due to the strong electron-withdrawing effect of the fluorine atoms the role of the negative charge of the dissociated PFAAs is likely insignificant.			●					●	-		B	-
436	蓄積性	Gebbink, Wouter A; Bignert, Anders; Berger, Urs	Perfluoroalkyl acids (PFAAs) and selected precursors in the Baltic seaenvironment: do precursors play a role in food web accumulation of PFAAs	2016	Environ Sci Technol. 2016 Jun 21;50(12):6354-62. doi: 10.1021/acs.est.6b01197. Epub 2016 Jun 1.	The present study examined the presence of perfluoroalkyl acids (PFAAs) and selected precursors in the Baltic Sea abiotic environment and guillemot food web, and investigated the relative importance of precursors in food web accumulation of PFAAs. Sediment, water, zooplankton, herring, sprat, and guillemot eggs were analyzed for perfluoroalkane sulfonic acids (PFSAs; C4,6,8,10) and perfluoroalkyl carboxylic acids (PFCAs; C6-15) along with six perfluoro-octane sulfonic acid (PFOS) precursors and 11 polyfluoroalkyl phosphoric acid diesters (diPAPs). FOSA, FOSAA and its methyl and ethyl derivatives (Me- and EtFOSAA), and 6:2/6:2 diPAP were detected in sediment and water. While FOSA and the three FOSAAs were detected in all biota, a total of nine diPAPs were only detected in zooplankton. Concentrations of PFOS precursors and diPAPs exceeded PFOS and PFCA concentrations, respectively, in zooplankton, but not in fish and guillemot eggs. Although PFOS precursors were present at all trophic levels, they appear to play a minor role in food web accumulation of PFOS based on PFOS precursor/PFOS ratios and PFOS and FOSA isomer patterns. The PFCA pattern in fish could not be explained by the intake pattern based on PFCAs and analyzed precursors, that is, diPAPs. Exposure to additional precursors might therefore be a dominant exposure pathway compared to direct PFCA exposure for fish.			●						-		B	-
437	蓄積性	Ghisi, Rossella; Vamerali, Teofilo; Manzetti, Sergio	Accumulation of perfluorinated alkyl substances (PFAS) in agricultural plants: a review	2019	Environ Res. 2019 Feb;169:326-341. doi: 10.1016/j.envres.2018.10.023. Epub 2018 Oct 30.	PFASs are a class of compounds that include perfluoroalkyl and polyfluoroalkyl substances, some of the most persistent pollutants still allowed - or only partially restricted - in several product fabrications and industrial applications worldwide. PFASs have been shown to interact with blood proteins and are suspected of causing a number of pathological responses, including cancer. Given this threat to living organisms, we carried out a broad review of possible sources of PFASs and their potential accumulation in agricultural plants, from where they can transfer to humans through the food chain. Analysis of the literature indicates a direct correlation between PFAS concentrations in soil and bioaccumulation in plants. Furthermore, plant uptake largely changes with chain length, functional group, plant species and organ. Low accumulations of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS) have been found in peeled potatoes and cereal seeds, while short-chain compounds can accumulate at high levels in leafy vegetables and fruits. Significant variations in PFAS buildup in plants according to soil amendment are also found, suggesting a particular interaction with soil organic matter. Here, we identify a series of challenges that PFASs pose to the development of a safe agriculture for future generations.			●						-		B	-
438	蓄積性	Goeritz, Ina; Falk, Sandy; Stahl, Thorsten; Schäfers, Christoph; Schlechtriem, Christian	Biomagnification and tissue distribution of perfluoroalkyl substances (PFASs) in market-size rainbow trout (Oncorhynchus mykiss)	2013	Environ Toxicol Chem. 2013 Sep;32(9):2078-88. doi: 10.1002/etc.2279. Epub 2013 Jul 12.	The present study investigated the biomagnification potential as well as the substance and tissue-specific distribution of perfluoroalkyl substances (PFASs) in market-size rainbow trout (Oncorhynchus mykiss). Rainbow trout with an average body weight of 314 ± 21 g were exposed to perfluorobutane sulfonate (PFBS), perfluorohexane sulfonate (PFHxS), perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), and perfluorononanoic acid (PFNA) in the diet for 28 d. The accumulation phase was followed by a 28-d depuration phase, in which the test animals were fed with nonspiked trout feed. On days 0, 7, 14, 28, 31, 35, 42, and 56 of the present study, fish were sampled from the test basin for PFAS analysis. Biomagnification factors (BMFs) for all test compounds were determined based on a kinetic approach. Distribution factors were calculated for each test compound to illustrate the disposition of PFASs in rainbow trout after 28 d of exposure. Dietary exposure of market-size rainbow trout to PFASs did not result in biomagnification; BMF values were calculated as 0.42 for PFOS, >0.23 for PFNA, >0.18 for PFHxS, >0.04 for PFOA, and >0.02 for PFBS, which are below the biomagnification threshold of 1. Liver, blood, kidney, and skin were identified as the main target tissues for PFASs in market-size rainbow trout. Evidence was shown that despite relative low PFAS contamination, the edible parts of the fish (the fillet and skin) can significantly contribute to the whole-body burden.			●						-		B	-
439	蓄積性	Houde, Magali; De Silva, Amila O; Muir, Derek C G; Letcher, Robert J	Monitoring of perfluorinated compounds in aquatic biota: an updated review	2011	Environ Sci Technol. 2011 Oct 1;45(19):7962-73. doi: 10.1021/es104326w. Epub 2011 May 4.	The goal of this article is to summarize new biological monitoring information on perfluorinated compounds (PFCs) in aquatic ecosystems (post-2005) as a followup to our critical review published in 2006. A wider range of geographical locations (e.g., South America, Russia, Antarctica) and habitats (e.g., high-mountain lakes, deep-ocean, and offshore waters) have been investigated in recent years enabling a better understanding of the global distribution of PFCs in aquatic organisms. High concentrations of PFCs continue to be detected in invertebrates, fish, reptiles, and marine mammals worldwide. Perfluorooctane sulfonate (PFOS) is still the predominant PFC detected (mean concentrations up to 1900 ng/g ww) in addition to important concentrations of long-chain perfluoroalkyl carboxylates (PFCAs; sum PFCAs up to 400 ng/g ww). More studies have evaluated the bioaccumulation and biomagnification of these compounds in both freshwater and marine food webs. Several reports have indicated a decrease in PFOS levels over time in contrast to PFCA concentrations that have tended to increase in tissues of aquatic organisms at many locations. The detection of precursor metabolites and isomers has become more frequently reported in environmental assessments yielding important information on the sources and distribution of these contaminants. The integration of environmental/ecological characteristics (e.g., latitude/longitude, salinity, and/or trophic status at sampling locations) and biological variables (e.g., age, gender, life cycle, migration, diet composition, growth rate, food chain length, metabolism, and elimination) are essential elements in order to adequately study the environmental fate and distribution of PFCs and should be more frequently considered in study design.			●						-		B	-
440	蓄積性	Kratzer J, Ahrens L, Roos A, Bäcklin BM, Ebinghaus R.	Temporal trends of poly € fluoroalkyl compounds (PFCs) in liver tissue of grey seals (Halichoerus grypus) from the Baltic Sea, 1974 –2008	2011	Chemosphere. 2011 Sep;84(11):1592-600. doi: 10.1016/j.chemosphere.2011.05.036. Epub 2011 Jun 15.	Temporal trends of polyfluoroalkyl compounds (PFCs) were examined in grey seal (Halichoerus grypus) liver from the Baltic Sea over a period of 35 years (1974-2008). In total, 17 of 43 PFCs were found, including the perfluoroalkyl sulfonates (C(4)-C(10) PFSAs), perfluorooctanesulfinate (PFOSi), long chain perfluoroalkyl carboxylates (C(7)-C(14) PFCAs), and perfluoroalkyl sulfonamides (i.e., perfluorooctane sulfonamide (FOSA) and N-ethyl perfluorooctane sulfonamide (EtFOSA)), whereas saturated and unsaturated fluorotelomer carboxylates, shorter chain PFCAs and perfluoroalkyl phosphonic acids were not detected. Perfluorooctane sulfonate (PFOS) was the predominant compound (9.57-1,444 ng g(-1) wet weight (ww)), followed by perfluorononanoate (PFNA, 0.47-109 ng g(-1) ww). C(6)-C(8) PFSAs, PFOSi and C(7)-C(13) PFCAs showed statistically significant increasing concentrations between 1974 and 1997, with a peak in 1997 and then decreased or levelled off (except for C(12) and C(13) PFCAs). FOSA had a different temporal trend with a maximum in 1989 followed by significant decreasing concentrations until 2008. Toxicological implications for grey seals are limited, but the maximal PFOS concentration found in this study was about 40 times lower than the predicted lowest observed effect concentrations (LOEC). The statistically significant decreasing concentrations or levelling off for several PFCs in the relative closed marine ecosystem of the Baltic Sea indicate a rapidly responding to reduced emissions to the marine environment. However, the high concentrations of PFOS and continuing increasing concentrations of the longer chain PFCAs (C(12)-C(14)) shows that further work on the reduction of environmental emissions of PFCs are necessary.			●						-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献①ラン	文献②ラン
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
441	蓄積性	Martin, Jonathan W; Mabury, Scott A; Solomon, Keith R; Muir, Derek C G	Dietary accumulation of perfluorinated acids in juvenile rainbow trout (Oncorhynchus Mykiss)	2003	Environ Toxicol Chem. 2003 Jan;22(1):189-95. doi: 10.1002/etc.5620220125	Perfluorinated acids (PFAs) recently have emerged as persistent global contaminants after their detection in wildlife and humans from various geographic locations. The highest concentrations of perfluorooctane sulfonate are characteristically observed in high trophic level organisms, indicating that PFAs may have a significant bioaccumulation potential. To examine this phenomenon quantitatively, we exposed juvenile rainbow trout (Oncorhynchus mykiss) simultaneously to a homologous series of perfluoroalkyl carboxylates and sulfonates for 34 d in the diet, followed by a 41-d depuration period. Carcass and liver concentrations were determined by using liquid chromatography-tandem mass spectrometry, and kinetic rates were calculated to determine compound-specific bioaccumulation parameters. Depuration rate constants ranged from 0.02 to 0.23/d, and decreased as the length of the fluorinated chain increased. Assimilation efficiency was greater than 50% for all test compounds, indicating efficient absorption from food. Bioaccumulation factors (BAFs) ranged from 0.038 to 1.0 and increased with length of the perfluorinated chain; however, BAFs were not statistically greater than 1 for any PFA. Sulfonates bioaccumulated to a greater extent than carboxylates of equivalent perfluoroalkyl chain length, indicating that hydrophobicity is not the sole determinant of PFA accumulation potential and that the acid function must be considered. Dietary exposure will not result in biomagnification of PFAs in juvenile trout, but extrapolation of these bioaccumulation parameters to larger fish and homeothermic organisms should not be performed.			●							-		B	-
442	蓄積性	Martin, Jonathan W; Mabury, Scott A; Solomon, Keith R; Muir, Derek C G	Bioconcentration and tissue distribution of perfluorinated acids in rainbow trout (Oncorhynchus Mykiss)	2003	Environ Toxicol Chem. 2003 Jan;22(1):196-204. doi: 10.1002/etc.5620220126	Rainbow trout (Oncorhynchus mykiss) were exposed simultaneously to a homologous series of perfluoroalkyl carboxylates and sulfonates in a flow-through system to determine compound-specific tissue distribution and bioconcentration parameters for perfluorinated acids (PFAs). In general, PFAs accumulated to the greatest extent in blood > kidney > liver > gall bladder. Carboxylates and sulfonates with perfluoroalkyl chain lengths shorter than seven and six carbons, respectively, could not be detected in most tissues and were considered to have insignificant bioconcentration factors (BCFs). For detectable PFAs, carcass BCFs increased with increasing length of the perfluoroalkyl chain, ranging from 4.0 to 23,000, based on wet weight concentrations. Carboxylate carcass BCFs increased by a factor of eight for each additional carbon in the perfluoroalkyl chain between 8 and 12 carbons, but this relationship deviated from linearity for the longest PFA tested, possibly because of decreased gill permeability. In general, half-lives (3.9-28 d) and uptake rates (0.053-1.700 L/kg/d) also increased with increasing length of the perfluoroalkyl chain in all tissues. Sulfonates had greater BCFs, half-lives, and rates of uptake than the corresponding carboxylate of equal perfluoroalkyl chain length, indicating that hydrophobicity, as predicted by the critical micelle concentration, is not the only determinant of PFA bioaccumulation potential and that the acid function must be considered.			●							-		B	-
443	蓄積性	Müller, Claudia E; De Silva, Amila O; Small, Jeff; Williamson, Mary; Wang, Xiaowa; Morris, Adam; Katz, Sharon; Gamberg, Mary; Muir, Derek C G	Biomagnification of perfluorinated compounds in a remote terrestrial food chain: Lichen-Caribou-Wolf	2011	Environ Sci Technol. 2011 Oct 15;45(20):8665-73. doi: 10.1021/es201353v. Epub 2011 Sep 9.	The biomagnification behavior of perfluorinated carboxylates (PFCAs) and perfluorinated sulfonates (PFSAs) was studied in terrestrial food webs consisting of lichen and plants, caribou, and wolves from two remote northern areas in Canada. Six PFCAs with eight to thirteen carbons and perfluorooctane sulfonate (PFOS) were regularly detected in all species. Lowest concentrations were found for vegetation (0.02-0.26 ng/g wet weight (ww) sum (Σ) PFCAs and 0.002-0.038 ng/g ww PFOS). Wolf liver showed highest concentrations (10-18 ng/g ww ΣPFCAs and 1.4-1.7 ng/g ww PFOS) followed by caribou liver (6-10 ng/g ww ΣPFCAs and 0.7-2.2 ng/g ww PFOS). Biomagnification factors were highly tissue and substance specific. Therefore, individual whole body concentrations were calculated and used for biomagnification and trophic magnification assessment. Trophic magnification factors (TMF) were highest for PFCAs with nine to eleven carbons (TMF = 2.2-2.9) as well as PFOS (TMF = 2.3-2.6) and all but perfluorooctanoate were significantly biomagnified. The relationship of PFCA and PFSA TMFs with the chain length in the terrestrial food chain was similar to previous studies for Arctic marine mammal food web, but the absolute values of TMFs were around two times lower for this study than in the marine environment. This study demonstrates that challenges remain for applying the TMF approach to studies of biomagnification of PFCAs and PFSAs, especially for terrestrial animals.			●							-		B	-
444	蓄積性	Peng, Hui; Zhang, Shiyi; Sun, Jianxian; Zhang, Zhong; Giesy, John P; Hu, Jianying	Isomer-Specific Accumulation of Perfluorooctanesulfonate from (N-Ethyl perfluorooctanesulfonamido) ethanol-based Phosphate Diester in Japanese Medaka (Oryzias latipes)	2014	Environ Sci Technol. 2014 Jan 21;48(2):1058-66. doi: 10.1021/es404867w. Epub 2014 Jan 8.	While (N-ethyl perfluorooctanesulfonamido)ethanol (FOSE) -based phosphate diester (diSPAP) has been proposed as a candidate precursor of perfluorooctanesulfonate (PFOS), its potential biotransformation to PFOS has not been verified. Metabolism of diSPAP was investigated in Japanese medaka (Oryzias latipes) after exposure in water for 10 days, followed by 10 days of depuration. Branched isomers of diSPAP (B-diSPAP) were preferentially enriched in medaka exposed to diSPAP, with the proportion of branched isomers (BF) ranging from 0.56 to 0.80, which was significantly greater than that in the water to which the medaka were exposed (0.36) ($p < 0.001$). This enrichment was due primarily to preferential uptake of B-diSPAP. PFOS together with perfluorooctanesulfonamide (PFOSA), N-ethyl perfluorooctanesulfonamide (NEtFOSA), 2-(perfluorooctanesulfonamido)acetic acid (FOSAA), NEtFOSAA, FOSE, and NEtFOSE were detected in medaka exposed to diSPAP, which indicated the potential for biotransformation of diSPAP to PFOS via multiple intermediates. Due to preferential metabolism of branched isomers, FOSAA and PFOSA exhibited greater BF values (>0.5) than those of NEtFOSA, NEtFOSAA, and NEtFOSE (<0.2). Such preferential metabolism of branched isomers along the primary pathway of metabolism and preferential accumulation of B-diSPAP led to enrichment of branched PFOS (B-PFOS) in medaka. Enrichment of B-PFOS was greater for 3-, 4-, and 5-perfluoromethyl PFOS (P3MPFOS, P4MPFOS, and P5MPFOS), for which values of BF were 0.58 ± 0.07, 0.62 ± 0.06, and 0.61 ± 0.05 (day 6), respectively; these values are 5.8-, 7.8-, and 6.4-fold greater than those of technical PFOS. This work provides evidence on the isomer-specific accumulation of PFOS from diSPAP and will be helpful to track indirect sources of PFOS in the future.			●							-		B	-
445	蓄積性	Bossi, Rossana; Riget, Frank F; Dietz, Rune	Temporal and spatial trends of perfluorinated compounds in ringed seal (Phoca hispida) from Greenland	2005	Environ Sci Technol. 2005 Oct 1;39(19):7416-22. doi: 10.1021/es0508469.	Perfluorinated compounds (PFCs), such as perfluorooctane sulfonate (PFOS) and related compounds, have been identified as global pollutants and have shown their bioaccumulation into higher trophic levels in the food chain. PFCs have been found in remote areas far from sources, such as the Arctic. In this study spatial and temporal trends in the concentrations of selected PFCs were measured using archived liver samples of ringed seal (Phoca hispida) from East and West Greenland. The samples were collected in four different years at each location, between 1986 and 2003 in East Greenland and between 1982 and 2003 in West Greenland. PFOS was the major contributor to the burden of PFCs in samples, followed by perfluoroundecanoic acid (PFUnA). Perfluorononanoic acid (PFNA) and perfluorodecanoic acid (PFDA) were also detected in most samples. Perfluorohexane sulfonate (PFHxS) and perfluorooctane sulfonamide (PFOSA) were only found sporadically. Perfluorooctanoic acid was not found in detectable concentrations in any sample. Regression analysis of logarithmic transformed PFOS, PFDA, and PFUnA median concentrations indicated a significant temporal trend with increasing concentrations at both locations. A spatial trend in PFOS concentrations (ANOVA, $p < 0.0001$) was observed between the two sampling locations, with significantly higher concentrations in seals from East Greenland.				●						-		B	-
446	蓄積性	Butt, Craig M; Mabury, Scott A; Muir, Derek C G; Braune, Birgit M	Prevalence of long-chained perfluorinated carboxylates in seabirds from the Canadian Arctic between 1975 and 2004	2007	Environ Sci Technol. 2007 May 15;41(10):3521-8. doi: 10.1021/es062710w.	Temporal trends in perfluoroalkyl compounds (PFCs) were investigated in liver samples from two seabird species, thick-billed murres (Uria lomvia) and northern fulmars (Fulmaris glacialis), from Prince Leopold Island in the Canadian Arctic. Thick-billed murre samples were from 1975, 1993, and 2004, whereas northern fulmars were from 1975, 1987, 1993, and 2003. Between 8 and 10 individuals were analyzed per year. Analytes included C7-C15 perfluorinated carboxylates (PFCAs) and their suspected precursors, the 8:2 & 10:2 fluorotelomer saturated and unsaturated carboxylates (FTCAs, FTUCAs), C6, C8 (perfluorooctane sulfonate, PFOS), C10 sulfonates, and perfluorooctane sulfonamide (PFOSA). Liver samples were homogenized, liquid-liquid extracted with methyl tert-butyl ether, cleaned-up using hexafluoropropanol, and analyzed by LC-MS/ MS. Overall, concentrations in seabirds were lower than those in other marine animals that occupy similar or higher trophic positions. In contrast to most other wildlife samples, PFC profiles were dominated by the PFCAs which comprised 81% and 93% of total PFC profiles in the 2004 thick-billed murre and 2003 northern fulmar samples, respectively. As well, the PFCA profiles were mainly comprised of the C11-C15 PFCAs, which appears to be unique among other wildlife species. PFC concentrations were found to increase significantly from 1975 to 2003/2004. Doubling times in thick-billed murres ranged from 2.3 yrs for perfluoropentadecanoate (PFPA) to 9.9 yrs for perfluorododecanoate (PFDoA), and from 2.5 yrs for PFPA to 11.7 yrs for perfluorodecanoate (PFDA) in northern fulmars. PFCA concentration increases in thick-billed murres were significant for both time periods (1975-1993, 1993-2004), but in northern fulmars appeared to remain steady after 1993. Differences in the temporal trends observed may be the result of differing migratory patterns of the seabirds. Finally, the detection of the 8:2 and 10:2 FTUCAs in seabirds is suggestive of fluorotelomer alcohols as a source of some PFCAs.				●						-		B	-
447	蓄積性	Butt, Craig M; Muir, Derek C G; Stirling, Ian; Kwan, Michael; Mabury, Scott A	Rapid response of arctic ringed seals to changes in perfluoroalkyl production	2007	Environ Sci Technol. 2007 Jan 1;41(1):42-9. doi: 10.1021/es061267m.	Temporal trends in perfluoroalkyl compounds (PFCs) were investigated in liver samples from two ringed seal (Phoca hispida) populations in the Canadian Arctic, Arviat (Western Hudson Bay) (1992, 1998, 2004, 2005) and Resolute Bay (Lancaster Sound) (1972, 1993, 2000, 2004, 2005). PFCs analyzed included C7-C15 perfluorinated carboxylates (PFCAs) and their suspected precursors, the 8:2 and 10:2 fluorotelomer saturated and unsaturated carboxylates (FTCAs, FTUCAs), C4, C6, C8, C10 sulfonates, and perfluorooctane sulfonamide (PFOSA). Liver samples were homogenized, liquid-liquid extracted with methyl tert-butyl ether, cleaned up using hexafluoropropanol, and analyzed by liquid chromatography with negative electrospray tandem mass spectrometry (LC-MS/MS). C9-C15 PFCAs showed statistically significant increasing concentrations during 1992-2005 and during 1993-2005 at Arviat and Resolute Bay, respectively. Doubling times ranged from 19.4 to 15.8 years for perfluorododecanoate (PFDoA) to 10.0-7.7 years for perfluorononanoate (PFNA) at Arviat and Resolute Bay but were shorter when excluding the 2005 samples. Conversely, perfluorooctane sulfonate (PFOS) and PFOSA concentrations showed maximum concentrations during 1998 and 2000 at Arviat and Resolute Bay, with statistically significant decreases from 2000 to 2005. In the case of Arviat, two consecutive decreases were measured from 1998 to 2003 and from 2003 to 2005. PFOS disappearance half-lives for seals at Arviat and Resolute Bay were 3.2 and 4.6 years. These results indicate that the ringed seals and their food web are rapidly responding to the phase out of perfluorooctane sulfonyl fluoride based compounds by 3M in 2001. Further, the relatively short doubling times of the PFCAs and PFOS disappearance half-lives support the hypothesis of atmospheric transport as the main transport mechanism of PFCs to the arctic environment.				●						-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
448	蓄積性	Conder, Jason M; Hoke, Robert A; De Wolf, Watze; Russell, Mark H; Buck, Robert C	Are PFCAs bioaccumulative? A critical review and comparison with regulatory criteria and persistent lipophilic compounds	2008	Environ Sci Technol. 2008 Feb 15;42(4):995-1003. doi: 10.1021/es070895g.	Perfluorinated acids, including perfluorinated carboxylates (PFCAs), and perfluorinated sulfonates (PFASs), are environmentally persistent and have been detected in a variety of wildlife across the globe. The most commonly detected PFAS, perfluorooctane sulfonate (PFOS), has been classified as a persistent and bioaccumulative substance. Similarities in chemical structure and environmental behavior of PFOS and the PFCAs that have been detected in wildlife have generated concerns about the bioaccumulation potential of PFCAs. Differences between partitioning behavior of perfluorinated acids and persistent lipophilic compounds complicate the understanding of PFCA bioaccumulation and the subsequent classification of the bioaccumulation potential of PFCAs according to existing regulatory criteria. Based on available research on the bioaccumulation of perfluorinated acids, five key points are highlighted in this review: (1) bioconcentration and bioaccumulation of perfluorinated acids are directly related to the length of each compound's fluorinated carbon chain; (2) PFASs are more bioaccumulative than PFCAs of the same fluorinated carbon chain length; (3) PFCAs with seven fluorinated carbons or less (perfluorooctanoate (PFO) and shorter PFCAs) are not considered bioaccumulative according to the range of promulgated bioaccumulation,"B", regulatory criteria of 1000-5000 L/kg; (4) PFCAs with seven fluorinated carbons or less have low biomagnification potential in food webs, and (5) more research is necessary to fully characterize the bioaccumulation potential of PFCAs with longer fluorinated carbon chains (>7 fluorinated carbons), as PFCAs with longer fluorinated carbon chains may exhibit partitioning behavior similar to or greater than PFOS. The bioaccumulation potential of perfluorinated acids with seven fluorinated carbons or less appears to be several orders of magnitude lower than "legacy" persistent lipophilic compounds classified as bioaccumulative. Thus, although many PFCAs are environmentally persistent and can be present at detectable concentrations in wildlife, it is clear that PFCAs with seven fluorinated carbons or less (including PFO) are not bioaccumulative according to regulatory criteria.				●						-		B	-
449	蓄積性	Dai, Jiayin; Li, Ming; Jin, Yihe; Saito, Norimitsu; Xu, Muqi; Wei, Fuwen	Perfluorooctanesulfonate and perfluorooctanoate in red panda and giant panda from China	2006	Environ Sci Technol. 2006 Sep 15;40(18):5647-52. doi: 10.1021/es0609710.	Perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) are important perfluorochemicals (PFCs) in various applications. Recently, it has been shown that these compounds are widespread in the environment, wildlife, and humans. The giant panda and the red panda belong to the order Carnivora, but are highly specialized as bamboo feeders. Both species are considered rare and endangered. In this study, we report for the first time on levels of PFOS and PFOA in serum of the giant panda and the red panda captured in zoos and animal parks from six provinces in China. PFOS was the predominant compound in all panda samples measured (ranging from 0.80 to 73.80 microg/L for red panda and from 0.76 to 19.00 microg/L for giant panda). The PFOA level ranged from 0.33 to 8.20 microg/L for red panda, and from 0.32 to 1.56 microg/L for giant panda. There was a positive significant correlation between concentrations of PFOS and PFOA in the serum obtained from pandas. No age- or sex- related differences were observed in concentrations of the fluorochemicals in panda sera. Greater concentrations of the fluorochemicals were found for those individuals collected from zoos near urbanized or industrialized areas than for other areas. These data combined with other reported data suggest that there are large differences in distribution of perfluorinated compounds in terrestrial animals.				●						-		B	-
450	蓄積性	Houde, Magali; Bujas, Trevor A D; Small, Jeff; Wells, Randall S; Fair, Patricia A; Bossart, Gregory D; Solomon, Keith R; Muir, Derek C G	Biomagnification of perfluoroalkyl compounds in the bottlenose dolphin (Tursiops truncatus) food web	2006	Environ Sci Technol. 2006 Jul 1;40(13):4138-44. doi: 10.1021/es060233b.	The environmental distribution and the biomagnification of a suite of perfluoroalkyl compounds (PFCs), including perfluorooctane sulfonate (PFOS) and C8 to C14 perfluorinated carboxylates (PFCAs), was investigated in the food web of the bottlenose dolphin (Tursiops truncatus). Surficial seawater and sediment samples, as well as zooplankton, fish, and bottlenose dolphin tissue samples, were collected at two U.S. locations: Sarasota Bay, FL and Charleston Harbor, SC. Wastewater treatment plant (WWTP) effluents were also collected from the Charleston area (n = 4). A solid-phase extraction was used for seawater and effluent samples and an ion-pairing method was used for sediment and biotic samples. PFCs were detected in seawater (range <1-12 ng/L), sediment (range <0.01-0.4 ng/g wet weight (ww)), and zooplankton (range 0.06-0.3 ng/g ww). The highest PFC concentrations were detected in WWTP effluents, whole fish, and dolphin plasma and tissue samples in which PFOS, C8 and C10-PFCAs predominated in most matrices. Contamination profiles varied with location suggesting different sources of PFC emissions. Biomagnification factors (BMFs) ranged from <1 to 156 at Sarasota Bay and <1 to 30 at Charleston. Trophic magnification factors (TMFs) for PFOS and C8-C11 PFCAs indicated biomagnification in this marine food web. The results indicate that using plasma and liver PFC concentrations as surrogate to whole body burden in a top marine predator overestimates the BMFs and TMFs.				●						-		B	-
451	蓄積性	Houde, Magali; Wells, Randall S; Fair, Patricia A; Bossart, Greg D; Hohn, Aleta A; Rowles, Teri K; Sweeney, Jay C; Solomon, Keith R; Muir, Derek C G	Polyfluoroalkyl compounds in free-ranging bottlenose dolphins (Tursiops truncatus) from the Gulf of Mexico and the Atlantic Ocean	2005	Environ Sci Technol. 2005 Sep 1;39(17):6591-8. doi: 10.1021/es0506556.	Polyfluoroalkyl compounds (PFAs) have been used for decades in industrial and commercial products and are now detected worldwide. Concentrations of two major PFA groups, carboxylic acids (PFCAs) and sulfonic acids (PFSAs), were assessed in plasma of bottlenose dolphins from the Gulf of Mexico (Sarasota Bay, FL) and the Atlantic Ocean (Delaware Bay, NJ, Charleston, SC, Indian River Lagoon (IRL), FL, and Bermuda). Eight PFAs were detected in the plasma of all dolphins. Perfluorooctane sulfonate (PFOS) was the predominant compound at all locations (range from 49 ng/g wet weight (w.w.) in dolphins from Bermuda to 1171 ng/g w.w. in plasma of animals from Charleston). Sum of PFA concentrations were significantly higher in animals from Charleston compared to IRL, Sarasota Bay, and Bermuda. Concentrations of several PFAs were negatively associated with age in animals from IRL and Charleston. No differences between gender were observed for all compounds at all locations. An increase in PFA concentrations was associated with a decrease of blubber thickness in animals from Sarasota Bay and IRL. Fluorotelomer 8:2 and 10:2 unsaturated carboxylic acids (FTUCAs), known degradation products of fluorotelomer alcohols and suspected precursors to PFCAs, were detected for the first time at low concentrations in plasma of dolphins.				●						-		B	-
452	蓄積性	Kannan, Kurunthachalam; Choi, Jae-Won; Iseki, Naomasa; Senthilkumar, Kurunthachalam; Kim, Dong Hoon; Giesy, John P	Concentrations of perfluorinated acids in livers of birds from Japan and Korea	2002	Chemosphere. 2002 Oct;49(3):225-31. doi: 10.1016/s0045-6535(02)00304-1.	Livers of birds collected from Japan and Korea (n = 83) were analyzed to determine the concentrations of perfluorooctanesulfonate (PFOS), perfluorooctanesulfonamide (FOSA), perfluorooctanoic acid (PFOA) and perfluorohexanesulfonate (PFHS). PFOS was found in the livers of 95% of the birds analyzed at concentrations greater than the limit of quantitation (LOQ) of 10 ng/g, wet weight. The greatest concentration of PFOS of 650 ng/g, wet weight, was found in the liver of a common cormorant from the Sagami River in Kanagawa Prefecture. Concentrations of PFOS in bird livers from Japan and Korea were within the ranges of values reported for those from the United States and certain European countries. PFOA and PFHS were found in 5-10% of the samples analyzed. The greatest concentrations of PFOA and PFHS in bird livers were 21 and 34 ng/g, wet weight, respectively. FOSA was found in all the samples (n = 10) of cormorants collected from the Sagami River in Japan. The greatest concentration of FOSA in cormorant liver was 215 ng/g, wet weight. There was no significant correlation between the concentrations of PFOS and FOSA in cormorants collected from the Sagami River. These results suggested that the distribution of FOSA is localized. No age- or gender-specific differences in fluorochemical concentrations could be discerned in birds.				●						-		B	-
453	蓄積性	Kannan, Kurunthachalam; Corsolini, Simonetta; Falandysz, Jerzy; Oehme, Günter; Focardi, Silvano; Giesy, John P	Perfluorooctanesulfonate and related fluorinated hydrocarbons in marine mammals, fishes, and birds from coasts of the Baltic and the Mediterranean Seas	2002	Environ Sci Technol. 2002 Aug 1;36(15):3210-6. doi: 10.1021/es020519q.	Perfluorooctanesulfonate (PFOS; C8F17SO3-), perfluorooctanesulfonamide (FOSA; C8F17SO2NH2), perfluorohexanesulfonate (PFHxS; C6F13SO3-), and perfluorooctanoate (PFOA; C7F15CO2-) were detected in 175 samples of liver and blood of bluefin tuna (Thunnus thynnus), swordfish (Xiphias gladius), common cormorants (Phalacrocorax carbo), bottlenose dolphins (Tursiops truncatus), striped dolphins (Stenella coeruleoalba), common dolphins (Delphinus delphi), fin whales (Balenoptera physalus), and long-finned pilot whales (Globicephala melas) from the Italian coast of the Mediterranean Sea and in livers of ringed seals (Phoca hispida), gray seals (Halichoerus grypus), white-tailed sea eagles (Haliaeetus albicilla), and Atlantic salmon (Salmo salar) from coastal areas of the Baltic Sea. PFOS was detected in all of the wildlife species analyzed. Concentrations of PFOS in blood decreased in order of bottlenose dolphins > bluefin tuna > swordfish. Mean PFOS concentrations (61 ng/ g, wet wt) in cormorant livers collected from Sardinia Island in the Mediterranean Sea were less than the concentrations of PFOA (95 ng/g, wetwt). PFOS concentrations in cormorant livers were significantly correlated with those of PFOA. FOSA was found in 14 of 19 livers or blood samples of marine mammals from the Mediterranean Sea. The highest concentration of 878 ng FOSA/g, wet wt, was found in the liver of a common dolphin. Livers of ringed and gray seals from the Bothnian Bay in the Baltic Sea contained PFOS concentrations ranging from 130 to 1,100 ng/g, wet wt. No relationships between PFOS concentrations and ages of ringed or gray seals were observed. Concentrations of PFOS in livers of seals were 5.5-fold greater than those in corresponding blood. A significant positive correlation existed between the PFOS concentrations in liver and blood, which indicates that blood can be used for nonlethal monitoring of PFOS. Trend analysis of PFOS concentrations in livers of white-tailed sea eagles collected from eastern Germany and Poland since 1979 indicated an increase in concentrations during the 1990s. Livers of Atlantic salmons did not contain quantifiable concentrations of any of the fluorochemicals monitored. PFOS is a widespread contaminant in wildlife from the Baltic and the Mediterranean Seas, while FOSA and PFOA were detected only in certain locations indicating their sporadic spatial distribution.				●						-		B	-
454	蓄積性	Kannan, K; Franson, J C; Bowerman, W W; Hansen, K J; Jones, P D; Giesy, J P	Perfluorooctane sulfonate in fish-eating water birds including bald eagles and albatrosses	2001	Environ Sci Technol. 2001 Aug 1;35(15):3065-70. doi: 10.1021/es001935i.	Perfluorooctane sulfonate (PFOS) was measured in 161 samples of liver, kidney, blood, or egg yolk from 21 species of fish-eating water birds collected in the United States including albatrosses from Sand Island, Midway Atoll, in the central North Pacific Ocean. Concentrations of PFOS in the blood plasma of bald eagles collected fromthe midwestern United States ranged from 13 to 2,220 ng/mL (mean: 330 ng/mL), except one sample that did not contain quantifiable concentrations of PFOS. Concentrations of PFOS were greater in blood plasma than in whole blood. Among 82 livers from various species of birds from inland or coastal U.S. locations, Brandt's cormorant from San Diego, CA, contained the greatest concentration of PFOS (1,780 ng/g, wet wt). PFOS was also found in the sera of albatrosses from the central North Pacific Ocean at concentrations ranging from 3 to 34 ng/mL. Occurrence of PFOS in birds from remote marine locations suggests widespread distribution of PFOS and related fluorochemicals in the environment.				●						-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ラン①抽出	文献ラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
455	蓄積性	Kannan, K; Hansen, K J; Wade, T L; Giesy, J P	Perfluorooctane sulfonate in oysters, Crassostrea virginica, from the Gulf of Mexico and the Chesapeake Bay, USA	2002	Arch Environ Contam Toxicol. 2002 Apr;42(3):313-8. doi: 10.1007/s00244-001-0003-8.	Concentrations of perfluorooctane sulfonate (PFOS), a metabolite of several sulfonated perfluoroorganic compounds, were measured in oysters collected from 77 locations in the Gulf of Mexico and Chesapeake Bay of the United States. PFOS was detected in oysters collected from 51 of the 77 locations at concentrations ranging from < 42 to 1,225 ng/g on a dry weight basis. This study provides baseline data for future monitoring programs to examine long-term trends in concentrations of PFOS.				●						-		B	-
456	蓄積性	Kannan, K; Koistinen, J; Beckmen, K; Evans, T; Gorzelany, J F; Hansen, K J; Jones, P D; Helle, E; Nyman, M; Giesy, J P	Accumulation of perfluorooctane sulfonate in marine mammals	2001	Environ Sci Technol. 2001 Apr 15;35(8):1593-8. doi: 10.1021/es001873w.	Perfluorooctane sulfonate (PFOS) is a perfluorinated molecule that has recently been identified in the sera of nonindustrially exposed humans. In this study, 247 tissue samples from 15 species of marine mammals collected from Florida, California, and Alaskan coastal waters; and northern Baltic Sea; the Arctic (Spitsbergen); and Sable Island in Canada were analyzed for PFOS. PFOS was detected in liver and blood of marine mammals from most locations including those from Arctic waters. The greatest concentrations of PFOS found in liver and blood were 1520 ng/g wet wt in a bottlenose dolphin from Sarasota Bay, FL, and 475 ng/mL in a ringed seal from the northern Baltic Sea (Bothnian Sea), respectively. No age-dependent increase in PFOS concentrations in marine mammals was observed in the samples analyzed. The occurrence of PFOS in marine mammals from the Arctic waters suggests widespread global distribution of PFOS including remote locations.				●						-		B	-
457	蓄積性	Kannan, Kurunthachalam; Newsted, John; Halbrook, Richard S; Giesy, John P	Perfluorooctanesulfonate and related fluorinated hydrocarbons in mink and river otters from the United States	2002	Environ Sci Technol. 2002 Jun 15;36(12):2566-71. doi: 10.1021/es0205028.	Mink and otters are good integrators of their aquatic environments and useful sentinel species for determining exposure to environmental contaminants. In this study, perfluorooctanesulfonate (PFOS; C8F17SO3-), perfluorooctanesulfonamide (FOSA; C8F17SO2NH2), perfluorohexanesulfonate (PFHxS; C6F13SO3-), and perfluorooctanoate (PFOA; C7F15CO2-) were measured in livers of mink and river otters collected from various locations in the United States. PFOS was found in all mink livers analyzed. Frequencies of occurrence of FOSA, PFHxS, and PFOA were less. The greatest concentration of PFOS measured in liver of mink was 5140 ng/g, wet weight. Maximum concentrations of FOSA, PFHxS, and PFOA in mink livers were 590, 39, and 27 ng/g, wet weight, respectively. There were no significant positive relationships between concentrations of PFOS and PFHxS or PFOA in mink livers. Concentrations of PFOS were positively correlated with those of FOSA in mink livers from Illinois. There was no significant correlation between concentrations of PFOS and lipid content in mink livers. There were no age- or sex-related differences in the concentrations of fluorochemicals in mink livers. Greater concentrations are associated with those individuals collected near urbanized and/or industrialized areas. PFOS was detected in livers of all river otters collected from Washington and Oregon at concentrations ranging from 25 to 994 ng/g, wet wt.				●						-		B	-
458	蓄積性	Kannan, Kurunthachalam; Perrotta, Emily; Thomas, Nancy J	Association between perfluorinated compounds and pathological conditions in southern sea otters	2006	Environ Sci Technol. 2006 Aug 15;40(16):4943-8. doi: 10.1021/es060932o.	Concentrations of four perfluorinated contaminants, including perfluorooctanesulfonate (PFOS) and perfluorooctanoic acid (PFOA), were measured in liver tissue from 80 adult female sea otters collected from the California coast during 1992-2002. Concentrations of PFOS and PFOA were in the ranges of <1-884 and <5-147 ng/g, wet wt, respectively. Concentrations of PFOA in the livers of these sea otters were among the highest values reported for marine mammals to date. Liver tissue from 6 male sea otters also was analyzed and contained significantly higher concentrations of PFOS than did tissues from female otters. To examine the association between exposures and potential effects, concentrations of PFOS and PFOA were compared among the adult female otters that died from infectious diseases, noninfectious causes, and from apparent emaciation. Concentrations of both PFOA and PFOS were significantly higher in sea otters in the infectious disease category than in the noninfectious category. Concentrations of PFOS and PFOA were not significantly different between noninfectious and emaciated otters, suggesting that the poor nutritive (body) status of emaciated otters did not affectthe concentrations of perfluorochemicals in livers. Concentrations of PFOA increased significantly from 1992 to 2002, whereas PFOS concentrations increased from 1992to 1998 and then decreased after 2000. Significant association between infectious diseases and elevated concentrations of PFOS/PFOA in the livers of sea otters is a cause for concern and suggests the need for further studies.				●						-		B	-
459	蓄積性	Keller, Jennifer M; Kannan, Kurunthachalam; Taniyasu, Sachi; Yamashita, Nobuyoshi; Day, Rusty D; Arendt, Michael D; Segars, Al L; Kucklick, John R	Perfluorinated compounds in the plasma of loggerhead and Kemp's ridley sea turtles from the southeastern coast of the United States	2005	Environ Sci Technol. 2005 Dec 1;39(23):9101-8. doi: 10.1021/es050690c.	Perfluorinated compounds (PFCs) have been measured in blood of humans and wildlife and are considered globally distributed contaminants. We examined 12 PFCs in the plasma of 73 loggerhead sea turtles (Caretta caretta) and 6 Kemp's ridley sea turtles (Lepidochelys kempii) captured from inshore waters of Core Sound, North Carolina (NC), and offshore waters of South Carolina, Georgia, and Florida (SC-FL). Perfluorooctanesulfonate (PFOS) and perfluorooctanoic acid (PFOA) were the dominant compounds, with respective mean concentrations of 11.0 ng/mL and 3.20 ng/mL for loggerhead turtles and 39.4 ng/mL and 3.57 ng/mL for Kemp's ridley turtles. Mean PFOS concentrations were 2- to 12-fold higher than typical mean sigmaPCB concentrations (approximately 5 ng/g wet mass) measured previously in sea turtle blood. More than 79% of the samples had detectable levels of perfluorocarboxylates (PFCAs) with 8-12 carbons, whereas only 17% or less of samples had detectable levels of PFCAs with 6 or 7 carbons. No samples had detectable levels of PFCAs with 4 or 5 carbons. In loggerhead turtles, sigmaPFC concentrations were not influenced by sex ($p > 0.05$), but were higher in turtles captured from inshore waters of NC than in turtles from offshore waters of SC-FL ($p = 0.009$). A backward stepwise multiple regression model showed that sigmaPFC concentrations were (1) significantly higher in Kemp's ridley turtles than loggerhead turtles ($p < 0.0001$), (2) higher in larger turtles ($p = 0.018$; carapace length used as a proxy for age), and (3) higher in turtles captured toward the north ($p = 0.006$). These findings suggest that bioaccumulation of PFCs in sea turtles is influenced by species, age, and habitat.				●						-		B	-
460	蓄積性	Krippner, Johanna; Falk, Sandy; Brunn, Hubertus; Georgii, Sebastian; Schubert, Sven; Stahl, Thorsten	Accumulation potentials of perfluoroalkyl carboxylic acids (PFCAs) and perfluoroalkyl sulfonic acids (PFSAs) in maize (Zea mays)	2015	J Agric Food Chem. 2015 Apr 15;63(14):3646-53. doi: 10.1021/acs.jafc.5b00012. Epub 2015 Apr 7.	Uptake of perfluoroalkyl acids (PFAAs) by maize represents a potential source of exposure for humans, either directly or indirectly via feed for animals raised for human consumption. The aim of the following study was, therefore, to determine the accumulation potential of perfluoroalkyl carboxylic acids (PFCAs) and perfluoroalkyl sulfonic acids (PFSAs) in maize (Zea mays). Two different concentrations of PFAAs were applied as aqueous solution to the soil to attain target concentrations of 0.25 mg or 1.00 mg of PFAA per kg of soil. Maize was grown in pots, and after harvesting, PFAA concentrations were measured in the straw and kernels of maize. PFCA and PFSA concentrations of straw decreased significantly with increasing chain length. In maize kernels, only PFCAs with a chain length $\leq$ C8 as well as perfluorobutanesulfonic acid (PFBS) were detected. The highest soil-to-plant transfer for both straw and kernels was determined for short-chained PFCAs and PFSAs.				●						-		B	-
461	蓄積性	Liu, Yanwei; Ruan, Ting; Lin, Yongfeng; Liu, Aifeng; Yu, Miao; Liu, Runzeng; Meng, Mei; Wang, Yawei; Liu, Jiyan; Jiang, Guibin	Chlorinated polyfluoroalkyl ether sulfonic acids in marine organisms from Bohai Sea, China: Occurrence, temporal variations, and trophic transfer behavior	2017	Environ Sci Technol. 2017 Apr 18;51(8):4407-4414. doi: 10.1021/acs.est.6b06593. Epub 2017 Mar 29.	F-53B, the commercial product of chlorinated polyfluoroalkyl ether sulfonic acids (Cl-PFESAs), has been used in Chinese chrome plating industry for 30 years, and was recently identified in the environment, which caused great concerns. So far, limited investigations have been performed on their environmental occurrence, fate and impact. In this study, we demonstrated the wide occurrence of Cl-PFESAs and their trophic transfer behavior in marine organisms from Chinese Bohai Sea. 6:2 Cl-PFESA (<0.016-0.575 ng/g wet weight) was the dominant congener, and 8:2 Cl-PFESA (<0.022-0.040 ng/g) was occasionally detected. Compared to other perfluoroalkyl and polyfluoroalkyl substances (PFASs) of concern, the levels of Cl-PFESAs were relatively lower in marine organisms. Based on the comparative analysis of Cl-PFESA contamination in mollusk samples collected in 2010-2014, both the concentrations and detection frequencies of Cl-PFESAs tended to increase in this region. And this kind of chemicals were more vulnerable to be accumulated in marine organisms at relatively higher trophic levels. Similar to perfluorooctanesulfonate (PFOS) and the long chain perfluorinated carboxylates (PFCAs), 6:2 Cl-PFESA could be magnified along the food chain. Accordingly, the potential threat might be posed to the wildlife and human beings due to unintended exposure to Cl-PFESAs.				●						-		B	-
462	蓄積性	Verreault, Jonathan; Berger, Urs; Gabrielsen, Geir W	Trends of perfluorinated alkyl substances in herring gull eggs from two coastal colonies in northern Norway: 1983-2003	2007	Environ Sci Technol. 2007 Oct 1;41(19):6671-7. doi: 10.1021/es070723j.	The present study reports on concentrations, patterns, and temporal trends (1983, 1993, and 2003) of 16 perfluorinated alkyl substances (PFAS) in whole eggs of herring gulls (Larus argentatus) from two geographically isolated colonies in northern Norway. Perfluorooctane sulfonate (PFOS) was the predominant PFAS in all eggs with mean concentrations up to 42 ng/g wet weight (ww) in samples from 2003. Perfluorohexane sulfonate (PFHxS) and perfluorodecane sulfonate (PFDcS) were found at concentrations several orders of magnitude lower than PFOS. The general accumulation profile of perfluorocarboxylates (PFCAs) in herring gull eggs was characterized by high proportions of odd and long carbon (C) chain length compounds in which perfluoroundecanoate (C11) and perfluorotridecanoate (C13) dominated with mean concentrations up to 4.2 and 2.8 ng/g ww, respectively. In both colonies PFOS concentrations in eggs showed a nearly 2-fold significant increase from 1983 to 1993, followed by a leveling off up to 2003. A comparable trend was found for PFHxS, whereas PFDcS was found to increase also between 1993 and 2003. PFCA concentrations showed marked significant increases during 1983-1993 associated with either a weak rise post-1993 (C8- to C11-PFCAs), although nonsignificant, or leveling off (C12- and C13-PFCAs). However, the composition of individual PFCAs (C8 to C15) to the summed concentrations of those eight PFCAs highly differed between the colonies and sampling years investigated. Present results suggest that direct and indirect local- and/or remote-sourced inputs (atmospheric and waterborne) of PFCAs have changed over the last two decades in these two coastal areas of Northern Norway.				●						-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①抽出	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
463	蓄積性	Verreault, Jonathan; Houde, Magali; Gabrielsen, Geir W; Berger, Urs; Haukås, Marianne; Letcher, Robert J; Muir, Derek C G	Perfluorinated alkyl substances in plasma, liver, brain, and eggs of glaucous gulls (Larus hyperboreus) from the Norwegian Arctic	2005	Environ Sci Technol. 2005 Oct 1;39(19):7439-45. doi: 10.1021/es051097y.	Recent environmental surveys have ascertained the widespread occurrence of perfluorinated alkyl substances (PFAS) in tissues of wildlife from the Arctic. In the present study, we investigated the distribution of a suite of PFAS in plasma, liver, brain, and egg samples from adult glaucous gulls (Larus hyperboreus), an apex scavenger-predator seabird breeding in the Norwegian Arctic. Perfluorooctane sulfonate (PFOS) was the predominant PFAS in all samples and was present at concentrations that are the highest reported thus far in any arctic seabird species and populations. Among the body compartment/ tissue samples analyzed, PFOS was highest in plasma (48.1-349 ng/g wet weight (ww)), followed by liver approximately equal to egg > brain. Perfluorocarboxylic acids (PFCAs) with 8-15 carbon (C) atoms were found, with the highest concentrations determined in plasma (sum PFCA: 41.8-262 ng/g ww), whereas 5C- and 6C-PFCAs were below the limits of detection. Perfluorobutane sulfonate, perfluorooctane sulfonamide, and four saturated (8:2 FTCA and 10:2 FTCA) and unsaturated (8:2 FTUCA and 10:2 FTUCA) fluorotelomer carboxylic acids were not detected in any samples. Perfluorohexane sulfonate was measured at concentrations up to 2.71 ng/g ww. The accumulation profiles of PFCAs were characterized by high proportions of the long and odd-numbered carbon-chain-length compounds, namely perfluoroundecanoic (11C) and perfluorotridecanoic acid (13C), although their individual contribution differed between the matrixes analyzed. Current PFAS concentrations suggest a bioaccumulation potential in Norwegian arctic glaucous gulls that needs to be assessed as part of a broad organohalogen contaminant cocktail with potential for mediating biological processes in this vulnerable top-predator marine species.				●						-		B	-
464	蓄積性	Wang, Yuan; Yeung, Leo W Y; Taniyasu, Sachi; Yamashita, Nobuyoshi; Lam, James C W; Lam, Paul K S	Perfluorooctane sulfonate and other fluorochemicals in waterbird eggs from south China	2008	Environ Sci Technol. 2008 Nov 1;42(21):8146-51. doi: 10.1021/es8006386.	To our knowledge, this is the first study reporting concentrations of perfluorinated compounds (PFCs) in waterbird eggs in south China. Concentrations of 11 PFCs (PFOS, PFHxS, PFBS, PFOSA, PFDoDA, PFUnDA, PFDA, PFNA, PFOA, PFHpA, PFHxA) were measured in night heron, great egret, and little egret eggs from south China (Hong Kong, Xiamen, Quanzhou). PFOS was found to be the dominant PFC in the waterbird eggs. Total concentrations of the 11 PFCs in waterbird eggs ranged from 27.0 ng/g ww (great egret from Hong Kong) to 160 ng/g ww (night heron from Quanzhou). Significant differences in PFOS concentrations were found among species, but not among locations. The composition profiles of the individual PFCs among egg samples were generally similar. Positive correlations were found between PFOS and some of the PFCAs in the egg samples from Hong Kong. Concentrations of some of the PFCs were significantly correlated with total PCB concentrations reported in a previous study in the night heron egg samples, but not in the great egret samples. Preliminary risk assessment suggests that there is no immediate risk of a reduction in offspring survival in waterbirds in south China due to PFOS, but more information is needed on the potential effects of PFCs in waterbirds.				●						-		B	-
465	蓄積性	Houde M, De Silva AO, Muir DCG, Letcher RJ	Monitoring of perfluorinated compounds in aquatic biota: an updated review.	2011	Environ Sci Technol. 2011 Oct 1;45(19):7962-73. doi: 10.1021/es104326w. Epub 2011 May 4.	The goal of this article is to summarize new biological monitoring information on perfluorinated compounds (PFCs) in aquatic ecosystems (post-2005) as a followup to our critical review published in 2006. A wider range of geographical locations (e.g., South America, Russia, Antarctica) and habitats (e.g., high-mountain lakes, deep-ocean, and offshore waters) have been investigated in recent years enabling a better understanding of the global distribution of PFCs in aquatic organisms. High concentrations of PFCs continue to be detected in invertebrates, fish, reptiles, and marine mammals worldwide. Perfluorooctane sulfonate (PFOS) is still the predominant PFC detected (mean concentrations up to 1900 ng/g ww) in addition to important concentrations of long-chain perfluoroalkyl carboxylates (PFCAs; sum PFCAs up to 400 ng/g ww). More studies have evaluated the bioaccumulation and biomagnification of these compounds in both freshwater and marine food webs. Several reports have indicated a decrease in PFOS levels over time in contrast to PFCA concentrations that have tended to increase in tissues of aquatic organisms at many locations. The detection of precursor metabolites and isomers has become more frequently reported in environmental assessments yielding important information on the sources and distribution of these contaminants. The integration of environmental/ecological characteristics (e.g., latitude/longitude, salinity, and/or trophic status at sampling locations) and biological variables (e.g., age, gender, life cycle, migration, diet composition, growth rate, food chain length, metabolism, and elimination) are essential elements in order to adequately study the environmental fate and distribution of PFCs and should be more frequently considered in study design.								●		-		B	-
466	ヒト（発生毒性）	Alkhalawi, E.; Kasper-Sonnenberg, M.; Wilhelm, M.; Völkel, W.; Wittsiepe, J.	Perfluoroalkyl acids (PFAAs) and anthropometric measures in the first year of life: Results from the Duisburg Birth Cohort	2016	J Toxicol Environ Health A. 2016;79(22-23):1041-1049. doi: 10.1080/15287394.2016.1219552.	In the context of the Duisburg Birth Cohort, this retrospective cohort study provides results of internal exposure to perfluorooctanoic acid (PFOA), perfluorooctanesulfonic acid (PFOS), and perfluorohexanesulfonic acid (PFHxS) in 156 mother-child pairs, and investigates whether and to what extent in utero exposure of these chemicals at German background levels exerts an effect on newborn and infant weight and length, and weight in relation to length expressed by ponderal index, in order to examine whether any reduction in weight is disproportionate to length. The levels of PFOA, PFOS, and PFHxS were determined in 81 maternal and 83 umbilical cord stored frozen plasma samples and 105 umbilical cord blood samples. Calculated factors were used to convert umbilical cord values to maternal levels. Weights and lengths were retrieved at birth and at 1, 4, 6, and 12 mo from examination booklets and ponderal index (kg/m(3)) was calculated. Subsequently, correlations were assessed using multiple linear regressions and generalized estimation equations with each of the measures as a continuous outcome variable and with PFOA, PFOS, and PFHxS concentration quartiles as categorized predictor variables, while adjusting for relevant covariates. PFOA, PFOS, and PFHxS were generally within German background exposure levels. There was a significant association between PFOA, PFOS, and PFHxS concentration quartiles and decrease in ponderal index at birth but not weight or height. A nonsignificant negative association between exposure to all three compounds and birth weight was noted. Follow-up showed no sustained effect of the PFAA on anthropometric measures during the first year.	●	●		●			●		-		B	-
467	ヒト（発生毒性）	Anand-Ivell, R.; Cohen, A.; Nørgaard-Pedersen, B.; Jönsson, B. A. G.; Bonde, J. P.; Hougaard, D. M.; Lindh, C. H.; Toft, G.; Lindhard, M. S.; Ivell, R.	Amniotic fluid INSL3 measured during the critical time window in human pregnancy relates to cryptorchidism, hypospadias, and phthalate load: a large case-control study	2018	Front Physiol. 2018 Apr 24;9:406. doi: 10.3389/fphys.2018.00406. eCollection 2018.	The period of the first to second trimester transition in human pregnancy represents a sensitive window for fetal organogenesis, particularly in regard to the development of the male reproductive system. This is a time of relative analytical inaccessibility. We have used a large national biobank of amniotic fluid samples collected at routine amniocentesis to determine the impacts of exogenous endocrine disruptor load on specific fetal biomarkers at this critical time. While adrenal and testicular steroids are highly correlated, they are also mostly positively influenced by increasing phthalate load, represented by the metabolites 7cx-MMeHP and 5cx-MEPP, by perfluorooctane sulfonate (PFOS) exposure, and by smoking, suggesting an adrenal stress response. In contrast, the testis specific biomarkers insulin-like peptide 3 (INSL3) and androstenedione are negatively impacted by the phthalate endocrine disruptors. Using a case-control design, we show that cryptorchidism and hypospadias are both significantly associated with increased amniotic concentration of INSL3 during gestational weeks 13-16, and some, though not all steroid biomarkers. Cases are also linked to a specifically increased variance in the Leydig cell biomarker INSL3 compared to controls, an effect exacerbated by maternal smoking. No influence of phthalate metabolites or PFOS was evident on the distribution of cases and controls. Considering that several animal and human studies have shown a negative impact of phthalate load on fetal and cord blood INSL3, respectively, the present results suggest that such endocrine disruptors may rather be altering the relative dynamics of testicular development and consequent hormone production, leading to a desynchronization of tissue organization during fetal development. Being born small for gestational age appears not to impact on the testicular biomarker INSL3 in second trimester amniotic fluid.	●	●								-		C	-
468	ヒト（生殖毒性）	Arbuckle, T.; Kubwabo, C.; Walker, M.; Davis, K.; Lalonde, K.; Kosarac, I.; Wen, S.; Arnold, D. L.	Umbilical cord blood levels of perfluoroalkyl acids and polybrominated flame retardants	2013	Int J Hyg Environ Health. 2013 Mar;216(2):184-94. doi: 10.1016/j.ijheh.2012.03.004. Epub 2012 Apr 10.	Perfluoroalkyl acids (PFAAs) and polybrominated diphenyl ethers (PBDEs) are persistent organic pollutants representing two classes of environmental contaminants of toxicological concern, especially for infants. Canadian biomonitoring data on these chemicals are limited. The objectives of this study were to measure PFAAs and PBDEs in umbilical cord blood from approximately 100 hospital deliveries in Ottawa (Ontario, Canada) and examine associations with characteristics of the mother and infant. Geometric means were 1.469 ng/mL for perfluorooctanoate (PFOA) (95% confidence interval of 1.292-1.671 ng/mL), 4.443 ng/mL for perfluorooctane sulfonate (PFOS) (95% CI of 3.735-5.285 ng/mL), 0.359 ng/mL for perfluorononanoic acid (PFNA) (95% CI of 0.318-0.404 ng/mL), and 0.579 ng/mL for perfluorohexanesulfonate (PFHxS) (95% CI of 0.473-0.709 ng/mL). The final multiple regression models indicated that lower gravida, term gestational age, smoking during pregnancy and vaginal delivery were significantly associated with higher levels of PFOS. Similarly, a vaginal delivery was significantly associated with higher PFOA, while weak associations were found with lower gravida and birth weight less than 2500g. Furthermore, higher PFNA concentrations were significantly associated with older mothers, and vaginal delivery, while weakly associated with term gestational age. Elevated PFHxS concentrations were significantly associated with smoking during pregnancy and lower gravida. Similar to reports from other countries, the preponderant PBDE congener measured in the cord blood was PBDE-47. Questions remain on why various studies have reported conflicting results on the association between PFAAs and birth weight. Crown Copyright (C) 2012 Published by Elsevier GmbH. All rights reserved.	●	●			●	●	●		-		B	-
469	ヒト（生殖毒性）	Macpherson, S.; Foster, W. G.; Sathyanarayana, S.; Fisher, M.; Monnier, P.; Lanphear, B.; Muckle, G.; Fraser, W. D.	Prenatal Perfluoroalkyl Substances and Newborn Anogenital Distance in a Canadian Cohort	2020	Reprod Toxicol. 2020 Jun;94:31-39. doi: 10.1016/j.reprotox.2020.03.011. Epub 2020 Apr 10.	Exposure to the man-made chemicals perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS) and perfluorohexanesulfonate (PFHxS) is widespread. These perfluoroalkyl substances (PFASs) have been associated with androgenic endocrine-disrupting properties; however, the evidence is equivocal and few human studies have examined the association between prenatal exposure to PFASs and markers of androgenic endocrine disruption such as changes in anogenital distance (AGD). In the MIREC cohort, PFOA, PFOS and PFHxS were analyzed in first trimester maternal plasma. AGD was measured in 205 male and 196 female newborns. The change in estimate procedure was used to identify confounders by sex and AGD in multiple linear regression models. Geometric mean plasma concentrations (95% CI) for PFOA, PFOS and PFHxS were 1.71 (1.61, 1.81), 4.4 (4.18, 4.64) and 1.15 (1.06, 1.25) μg/L, respectively. A one-unit increase in natural log transformed PFOA was associated with a 1.36 mm (95% CI 0.30, 2.41) increase in anoscrotal distance, adjusting for household income, active smoking status during pregnancy and gestational age. However, when examined by quartiles, a non-monotonic pattern was observed with wide confidence intervals. No consistent patterns were observed between maternal PFAS concentrations and female AGDs. This study found no clear evidence that maternal plasma concentrations of PFOS, PFOA or PFHxS were associated with shorter infant anogenital distance in males or any change in AGD in females. Whether the positive association observed between longer anoscrotal distance and PFOA is real or would have any long-lasting effect on the reproductive health of males is unknown and needs to be investigated further.	●	●								-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
470	ヒト（発生毒性）	Ashley-Martin, J.; Dodds, L.; Arbuckle, T. E.; Bouchard, M. F.; Fisher, M.; Morriset, A. S.; Monnier, P.; Shapiro, G. D.; Ettinger, A. S.; Dallaire, R.; Taback, S.; Fraser, W.; Platt, R. W.	Maternal concentrations of perfluoroalkyl substances and fetal markers of metabolic function and birth weight	2017	Am J Epidemiol. 2017 Feb 1;185(3):185-193. doi: 10.1093/aje/kww213.	Perfluoroalkyl substances (PFAS) are ubiquitous, persistent chemicals that have been widely used in the production of common household and consumer goods for their nonflammable, lipophobic, and hydrophobic properties. Inverse associations between maternal or umbilical cord blood concentrations of perfluorooctanoic acid and perfluorooctanesulfonate and birth weight have been identified. This literature has primarily examined each PFAS individually without consideration of the potential influence of correlated exposures. Further, the association between PFAS exposures and indicators of metabolic function (i.e., leptin and adiponectin) has received limited attention. We examined associations between first-trimester maternal plasma PFAS concentrations and birth weight and cord blood concentrations of leptin and adiponectin using data on 1705 mother-infant pairs from the Maternal Infant Research on Environmental Chemicals (MIREC) Study, a trans-Canada birth cohort study that recruited women between 2008 and 2011 Bayesian hierarchical models were used to quantify associations and calculate credible intervals. Maternal perfluorooctanoic acid concentrations were inversely associated with birth weight z score, though the null value was included in all credible intervals (log10 β = −0.10, 0.95 credible interval: −0.34, 0.13). All associations between maternal PFAS concentrations and cord blood adipocytokine concentrations were of small magnitude and centered around the null value. Follow-up in a cohort of children is required to determine how the observed associations manifest in childhood.	●	●		●	●	●				-		B	-
471	ヒト（発生毒性）	Ashley-Martin, J.; Dodds, L.; Arbuckle, T. E.; Morisset, A. S.; Fisher, M.; Bouchard, M. F.; Shapiro, G. D.; Ettinger, A. S.; Monnier, P.; Dallaire, R.; Taback, S.; Fraser, W.	Maternal and Neonatal Levels of Perfluoroalkyl Substances in Relation to Gestational Weight Gain	2016	Int J Environ Res Public Health. 2016 Jan 20;13(1):146. doi: 10.3390/ijerph13010146.	Perfluoroalkyl substances (PFASs) are ubiquitous, persistent pollutants widely used in the production of common household and consumer goods. There is a limited body of literature suggesting that these chemicals may alter metabolic pathways and growth trajectories. The relationship between prenatal exposures to these chemicals and gestational weight gain (GWG) has received limited attention. One objective was to analyze the associations among maternal plasma levels of three common perfluoroalkyl substances (perfluorooctanoate (PFOA), perfluorooctanesulfonate (PFOS), perfluorohexanesulfanoate (PFHxS)) and GWG. Additionally, we explored whether GWG was associated with cord blood PFAS levels. This study utilized data collected in the Maternal-Infant Research on Environmental Chemicals (MIREC) Study, a trans-Canada cohort study of 2001 pregnant women. Our analysis quantified associations between -1 maternal PFAS concentrations and GWG and -2 GWG and cord blood PFAS concentrations. Maternal PFOS concentrations were positively associated with GWG (β = 0.39 0.95 CI: 0.02, 0.75). Interquartile increases in GWG were significantly associated with elevated cord blood PFOA (OR = 1.33; 0.95 CI: 1.13 to 1.56) and PFOS (OR = 1.20; 0.95 CI: 1.03 to 1.40) concentrations. No statistically significant associations were observed between GWG and either measure of PFHxS. These findings warrant elucidation of the potential underlying mechanisms.	●	●		●						-		B	-
472	ヒト（生殖毒性）	Avanasi, R.; Shin, H. M.; Vieira, V. M.; Bartell, S. M.	Impacts of geocoding uncertainty on reconstructed PFOA exposures and their epidemiological association with preeclampsia	2016	Environ Res. 2016 Nov;151:505-512. doi: 10.1016/j.envres.2016.08.019. Epub 2016 Aug 25.	Many epidemiology studies have investigated associations of perfluorooctanoate (PFOA) exposures with a variety of adverse health outcomes for participants in the C8 Health Project. The exposure concentrations (i.e., air and groundwater) used in these studies were determined primarily based on participant's residential locations. However, for residential addresses that could not be geocoded to the street level, the exposure concentrations were assigned based on population-weighted ZIP code centroid, which may result in exposure mischaracterization. The aim of this current study is to evaluate the potential impact of mischaracterized exposure concentrations due to geocoding uncertainty on the predicted serum PFOA concentrations and the epidemiological association between PFOA exposure and preeclampsia. For both workplace addresses and incompletely geocoded residential addresses, we used Monte Carlo (MC) simulation to assign alternate geographic locations within the reported ZIP code (instead of population-weighted ZIP code centroids) and the corresponding exposure concentrations. We found that mischaracterization of residential exposure due to population-weighted ZIP code centroid assignment had no significant impact on the serum PFOA concentration predictions and the epidemiological association of PFOA exposure with preeclampsia. In contrast, the uncertainty in workplace exposure moderately impacted the rank exposure among the participants. We observed a 0.41 increase in the average adjusted odds ratio of preeclampsia occurrence that may be due to differing proportions of cases -0.643 and controls -0.545 with workplace address geocodes during pregnancy. This finding suggests that differential exposure mischaracterization can be reduced by obtaining accurate exposure information such as street addresses and tap water consumption, for both workplaces and residences. The analysis we present is one approach for estimating the potential impacts of positional errors in a geocoding-based exposure assessment on exposure estimates and epidemiological study results.	●	●								-		C	-
473	ヒト（生殖毒性）	Avanasi, R.; Shin, H. M.; Vieira, V. M.; Bartell, S. M.	Variability and epistemic uncertainty in water ingestion rates and pharmacokinetic parameters, and impact on the association between perfluorooctanoate and preeclampsia in the C8 Health Project population	2016	Environ Res. 2016 Apr;146:299-307. doi: 10.1016/j.envres.2016.01.011. Epub 2016 Jan 19.	We recently utilized a suite of environmental fate and transport models and an integrated exposure and pharmacokinetic model to estimate individual perfluorooctanoate (PFOA) serum concentrations, and also assessed the association of those concentrations with preeclampsia for participants in the C8 Health Project (a cross-sectional study of over 69000 people who were environmentally exposed to PFOA near a major U.S. fluoropolymer production facility located in West Virginia). However, the exposure estimates from this integrated model relied on default values for key independent exposure parameters including water ingestion rates, the serum PFOA half-life, and the volume of distribution for PFOA. The aim of the present study is to assess the impact of inter-individual variability and epistemic uncertainty in these parameters on the exposure estimates and subsequently, the epidemiological association between PFOA exposure and preeclampsia. We used Monte Carlo simulation to propagate inter-individual variability/epistemic uncertainty in the exposure assessment and reanalyzed the epidemiological association. Inter-individual variability in these parameters mildly impacted the serum PFOA concentration predictions (the lowest mean rank correlation between the estimated serum concentrations in our study and the original predicted serum concentrations was 0.95) and there was a negligible impact on the epidemiological association with preeclampsia (no change in the mean adjusted odds ratio (AOR) and the contribution of exposure uncertainty to the total uncertainty including sampling variability was 7%). However, when epistemic uncertainty was added along with the inter-individual variability, serum PFOA concentration predictions and their association with preeclampsia were moderately impacted (the mean AOR of preeclampsia occurrence was reduced from 1.12 to 1.09, and the contribution of exposure uncertainty to the total uncertainty was increased up to 33%). In conclusion, our study shows that the change of the rank exposure among the study participants due to variability and epistemic uncertainty in the independent exposure parameters was large enough to cause a 0.25 bias towards the null. This suggests that the TRUE AOR of the association between PFOA and preeclampsia in this population might be higher than the originally reported AOR and has more uncertainty than indicated by the originally reported confidence interval.	●	●								-		C	-
474	ヒト（生殖毒性）	Bach, C.; Matthiesen, B.; Olsen,; Henriksen, B.	Conditioning on parity in studies of perfluoroalkyl acids and time to pregnancy: an example from the danish national birth cohort	2018	Environ Health Perspect. 2018 Nov;126(11):117003. doi: 10.1289/EHP1493.	BACKGROUND: Previous studies have investigated the associations between perfluoroalkyl acids (PFAAs) in women and time to pregnancy (TTP). Inconsistent results may be explained by differences in conditioning on parity.OBJECTIVES: We used causal directed acyclic graphs to illustrate potential confounding related to previous pregnancies and exposure measurement error due to differences in the interpregnancy interval in pregnancy-based studies that include parous women. We exemplified the potential importance of these issues using data from the Danish National Birth Cohort.METHODS: We used discrete time survival models to estimate associations between maternal plasma PFAAs in early pregnancy and TTP in 638 nulliparous and 613 parous women.RESULTS: PFAA quartiles were not associated with the TTP in nulliparous women. In parous women, higher PFAA quartiles were associated with longer TTP. The strongest associations were estimated for perfluorohexane sulfonate and perfluorooctane sulfonate. PFAA concentrations were higher in women with longer interpregnancy intervals. Accounting for the interpregnancy interval attenuated the estimated associations.CONCLUSIONS: Associations between PFAAs and TTP in parous women may be biased by confounders related to previous pregnancies and exposure measurement error. To avoid these biases, studies that include parous women may need to condition on a) common causes of PFAAs and the TTP in the index pregnancy, b) previous births (a descendant of a collider), c) PFAA levels or common causes of PFAA levels and the TTP in the previous pregnancy (to alleviate collider stratification bias caused by conditioning on previous births), and d) the interpregnancy interval (in pregnancy-based studies). Alternatives would be to restrict studies to nulliparous women or to use toxicokinetic modeling to correct exposure estimates in parous women. These recommendations may be extended to studies of other chemicals with similar toxicokinetic properties.	●	●	●							-		C	-
475	ヒト（生殖毒性）	Bach, C. C.; Bech, B. H.; Nohr, E. A.; Olsen, J.; Matthiesen, N. B.; Bonefeld-Jørgensen, E. C.; Bossi, R.; Henriksen, T. B.	Perfluoroalkyl acids in maternal serum and indices of fetal growth: The Aarhus Birth Cohort	2016	Environ Health Perspect. 2016 Jun;124(6):848-54. doi: 10.1289/ehp.1510046. Epub 2015 Oct 23.	BACKGROUND: Previous studies indicated an association between intrauterine exposure to perfluorooctane sulfonate (PFOS) or perfluorooctanoate (PFOA) and lower birth weight. However, these perfluoroalkyl acids (PFAAs) have to some extent been substituted by other compounds on which little is known.OBJECTIVES: We investigated the association between specific PFAAs and birth weight, birth length, and head circumference at birth.METHODS: We studied 1507 mothers and their children from the Aarhus Birth Cohort (2008-2013). Nulliparous women were included during pregnancy, and serum levels of 16 PFAAs were measured between 9 and 20 completed gestational weeks (96% within 13 weeks). For compounds with quantifiable values in > 0.5 of samples (7 compounds), we report the associations with birth weight, birth length, and head circumference at birth determined by multivariable linear regression.RESULTS: Estimated mean birth weights were lower among women with serum perfluorohexane sulfonate, perfluoroheptane sulfonate, and PFOS concentrations above the lowest exposure quartile, but we found no consistent monotonic dose-response patterns. These associations were stronger when the population was restricted to term births (n = 1,426). For PFOS, the birth weight estimates for the highest versus lowest quartile were -50 g (95% CI: -123, 23 g) in all births and -62 g (95% CI: -126, 3 g) in term births. For the other PFAAs, the direction of the associations was inconsistent, and no overall association with birth weight was apparent. No PFAAs were associated with birth length or head circumference at birth.CONCLUSIONS: Overall, we did not find strong or consistent associations between PFAAs and birth weight or other indices of fetal growth, though estimated mean birth weights were lower among those with exposures above the lowest quartile for some compounds.CITATION: Bach CC, Bech BH, Nohr EA, Olsen J, Matthiesen NB, Bonefeld-Jørgensen EC, Bossi R, Henriksen TB. 2016 Perfluoroalkyl acids in maternal serum and indices of fetal growth: the Aarhus Birth Cohort.	●	●	●	●			●			-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報対象抽出	文献①ラン	文献②ラン
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
476	ヒト（生殖毒性）	Bach, C. C.; Bech, B. H.; Nohr, E. A.; Olsen, J.; Matthiesen, N. B.; Bossi, R.; Uldbjerg, N.; Bonefeld-Jørgensen, E. C.; Henriksen, T. B.	Serum perfluoroalkyl acids and time to pregnancy in nulliparous women	2015	Environ Res. 2015 Oct;142:535-41. doi: 10.1016/j.envres.2015.08.007.	Background: Previous studies on the exposure to perfluoroalkyl acids (PFAAs) and female fertility have provided conflicting results. We aimed to investigate the association between several PFAAs and time to pregnancy among nulliparous women. Methods: From 2008 to 2013, we included 1372 women from the Aarhus Birth Cohort, Aarhus University Hospital, Denmark, who provided data on time to pregnancy and a blood sample before 20 gestational weeks. We measured the levels of 16 PFAAs in maternal serum and report data for seven compounds with quantifiable values in at least 50% of samples. Fecundability ratios according to PFAA levels (quartiles or continuous levels) were estimated by discrete-time survival analyses, adjusted for potential confounders. We further investigated the association between PFAAs and infertility (time to pregnancy>12 months or infertility treatment prior to the studied pregnancy) by multivariable logistic regression. Results: Median levels of perfluorooctane sulfonate and perfluorooctanoate were 8.3 and 2.0 ng/mL. Overall, no obvious associations were found between any PFAAs and fecundability or infertility. Adjusted fecundability ratios (95% confidence intervals) were 1.09 (0.92-1.29) for perfluorooctane sulfonate and 1.10 (0.93-1.30) for perfluorooctanoate (highest versus lowest quartile). Conclusions: We found no evidence of an association between present serum levels of PFAAs and longer time to pregnancy or infertility in nulliparous women. This study further adds to the sparse knowledge on PFAAs besides perfluorooctane sulfonate and perfluorooctanoate.	●	●	●	●						-		C	-
477	ヒト（生殖毒性）	Bach, C. C.; Liew, Z.; Bech, B. H.; Nohr, E. A.; Fei, C.; Bonefeld-Jorgensen, E. C.; Henriksen, T. B.; Olsen, J.	Perfluoroalkyl acids and time to pregnancy revisited: An update from the Danish National Birth Cohort	2015	Environ Health. 2015 Jul 7;14:59. doi: 10.1186/s12940-015-0040-9.	BACKGROUND: We previously demonstrated an association between plasma perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) and longer time to pregnancy (TTP) in a sample from the Danish National Birth Cohort (DNBC, 1996-2002). In this study we investigated this association in a new sample from the same cohort.METHODS: Sample 1 consisted of 440 women, and Sample 2 consisted of 1161 women from whom we previously published the associations between PFOS or PFOA and TTP. We performed sample-specific and pooled analyses using discrete-time survival analyses to estimate fecundability ratios according to PFOS and PFOA quartiles, adjusted for potential confounders chosen guided by a directed acyclic graph. We also estimated odds ratios for infertility (TTP > 12 months or infertility treatment) according to PFOS and PFOA by multivariable logistic regression.RESULTS: In Sample 1 PFOS was not associated with lower fecundability ratios or infertility, and there was a tendency towards longer TTP with increasing PFOA only in parous women. In Sample 2 previously reported associations were again seen. In the pooled analyses including both parous and nulliparous women fecundability ratios were 13-22 % lower for the three higher quartiles of PFOS or PFOA compared to the reference quartile.CONCLUSIONS: The pooled analyses were driven by the larger old sample, but we did not corroborate our previous finding of an association between high PFOS and longer TTP in the new sample. The tendency towards an association for PFOA and TTP in parous women may be due to reverse causation. Results from the new sample are more in line with the recent literature.	●	●		●						-		C	-
478	ヒト（生殖毒性）	Bangma, J.; Eaves, L. A.; Oldenburg, K.; Reiner, J. L.; Manuck, T.; Fry, R. C.	Identifying Risk Factors for Levels of Per- and Polyfluoroalkyl Substances (PFAS) in the Placenta in a High-Risk Pregnancy Cohort in North Carolina	2020	Environ Sci Technol. 2020 Jul 7;54(13):8158-8166. doi: 10.1021/acs.est.9b07102. Epub 2020 Jun 12.	Prenatal exposure to per- and polyfluoroalkyl substances (PFAS), a ubiquitous class of chemicals, is associated with adverse outcomes such as pre-eclampsia, low infant birth weight, and later-life adiposity. The objectives of this study were to examine PFAS levels in the placenta and identify sociodemographic risk factors in a high-risk pregnancy cohort (n = 122) in Chapel Hill, North Carolina. Of concern, PFOS, PFHxS, PFHpS, and PFUnA were detected above the reporting limit in 99, 75, 55, and 0.49 of placentas, respectively. Maternal race/ethnicity was associated with significant differences in PFUnA levels. While the data from this high-risk cohort did not provide evidence for an association with hypertensive disorders of pregnancy, fetal growth, or gestational age, the prevalence of detectable PFAS in the placenta suggests a need to biomonitor for exposure to PFAS during pregnancy. Future research should investigate factors underlying the differences in PFAS levels in association with a mother's race/ethnicity, as well as potential effects on pregnancy and child health.	●	●								-		B	-
479	ヒト（生殖毒性）	Bell, E. M.; Yeung, E. H.; Ma, W.; Kannan, K.; Sundaram, R.; Smarr, M. M.; Buck Louis, G. M.	Concentrations of endocrine disrupting chemicals in newborn blood spots and infant outcomes in the upstate KIDS study	2018	Environ Int. 2018 Dec;121(Pt 1):232-239. doi: 10.1016/j.envint.2018.09.005. Epub 2018 Sep 13.	BACKGROUND: Novel methodologies to quantify infant exposures to endocrine disrupting chemicals (EDCs) for population-based studies are needed.OBJECTIVES: We used newborn dried blood spots to quantify three EDCs and their associations with infant outcomes in the Upstate KIDS Cohort.METHODS: We measured bisphenol A (BPA), perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) in 2071 singleton and 1040 twin infants born to mothers in New York State. We log transformed concentrations after rescaling by their standard deviations and modeled each in relation to gestational age, birthweight, length, head circumference and Ponderal Index (PI) using linear regression techniques. All models were adjusted for maternal age, body mass index, education, infertility treatment and parity. Generalized estimating equations with robust standard errors were used to assess the associations for twins.RESULTS: Chemicals were largely quantified above the limits of detection (>99% for PFOS and PFOA; 0.9 for BPA). Overall, we observed no significant associations between PFASs and birth size irrespective of plurality of birth. However, among twins, BPA was associated with decreases in gestational age (adjusted β = -0.09 weeks; 0.95 Confidence Interval (CI): -0.16, -0.02) and birthweight (adjusted β = -32.52 g; 0.95 CI: -60.99, -4.05), head circumference (adjusted β = -0.18 cm; 0.95 CI: -0.38, -0.02) and increased PI in singletons (adjusted β = 0.02 cm; 0.95 CI: 0.004, 0.04).CONCLUSION: We observed negative associations between BPA and birth size in twins. Our findings demonstrate the feasibility of newborn dried blood spots for quantifying neonatal exposure at the population level.	●	●	●							-		B	-
480	ヒト（発生毒性）	Berg, V.; Nøst, T. H.; Pettersen, R. D.; Hansen, S.; Veyhe, A. S.; Jorde, R.; Odland, J. Ø.; Sandanger, T. M.	Persistent organic pollutants and the association with maternal and infant thyroid homeostasis: a multipollutant assessment	2017	Environ Health Perspect. 2017 Jan;125(1):127-133. doi: 10.1289/EHP152. Epub 2016 May 24.	BACKGROUND: Disruption of thyroid homeostasis has been indicated in human studies targeting effects of persistent organic pollutants (POPs). Influence on the maternal thyroid system by POPs is of special interest during pregnancy, as such effects could impair infant thyroid homeostasis.OBJECTIVES: We investigated the association between POPs and thyroid stimulating hormone (TSH) and thyroid hormones (THs) in mother and child pairs from the Northern Norway Mother-and-Child Contaminant Cohort Study (MISA).METHODS: Nineteen POPs and ten thyroid parameters were analysed in serum from 391 pregnant women in their second trimester. In addition, TSH concentrations in heel prick samples from the infants were analysed by the Norwegian Newborn Screening program. Association studies with a multipollutant approach were performed using multivariate analyses; partial least squares (PLS) regression, hierarchical clustering and principle component analysis (PCA).RESULTS: Several POPs were significantly associated to TSH and THs: i) PFOS was positively associated with TSH; ii) PCBs, HCB and nonachlors were inversely associated to T3, T4 and FT4; and, iii) PFDA and PFUnDA were inversely associated to T3 and FT3. After mutual adjustments for the other contaminants, only PFDA and PFUnDA remained significantly associated to T3 and FT3, respectively. Infants born by mothers within the highest TSH quartile had 0.1 higher mean concentrations of TSH compared to children born by mothers in the lowest TSH quartile.CONCLUSION: The present results suggest that background exposures to POPs can alter maternal thyroid homeostasis. This research contributes to the understanding of multipollutant exposures using multivariate statistical approaches and highlights the complexity of investigating environmental concentrations and mixtures in regards to maternal and infant thyroid function.	●	●	●	●						-		B	-
481	ヒト（発生毒性）	Bjerregaard-Olesen, C.; Bach, C. C.; Long, M.; Wielsøe, M.; Bech, B. H.; Henriksen, T. B.; Olsen, J.; Bonefeld-Jørgensen, E. C.	Associations of Fetal Growth Outcomes with Measures of the Combined Xenoestrogenic Activity of Maternal Serum Perfluorinated Alkyl Acids in Danish Pregnant Women	2019	Environ Health Perspect. 2019 Jan;127(1):17006. doi: 10.1289/EHP1884.	BACKGROUND: Higher concentrations of single perfluorinated alkyl acids (PFAAs) have been associated with lower birth weight (BW), but few studies have examined the combined effects of PFAA mixtures. PFAAs have been reported to induce estrogen receptor (ER) transactivity, and estrogens may influence human fetal growth. We hypothesize that mixtures of PFAAs may affect human fetal growth by disrupting the ER.OBJECTIVES: We aimed to study the associations between the combined xenoestrogenic activity of PFAAs in pregnant women's serum and offspring BW, length, and head circumference.METHODS: We extracted the actual mixture of PFAAs from the serum of 702 Danish pregnant women (gestational wk 11–13) enrolled in the Aarhus Birth Cohort (ABC) using solid phase extraction, high-performance liquid chromatography (HPLC), and weak anion exchange. PFAA-induced xenoestrogenic receptor transactivation (XER) was determined using the stable transfected MVLN cell line. Associations between XER and measures of fetal growth were estimated using multivariable linear regression with primary adjustment for maternal age, body mass index (BMI), educational level, smoking, and alcohol intake, and sensitivity analyses with additional adjustment for gestational age (GA) (linear and quadratic).RESULTS: On average, an interquartile range (IQR) increase in XER was associated with a 48 g [95% confidence interval (CI): −90, −6] decrease in BW and a 0.3 cm (95% CI: 0.1, 0.5) decrease in birth length. Upon additional adjustment for GA, the estimated mean differences were −28g (95% CI: −60, 4) and −0.2cm (95% CI: −0.4, 0.0), respectively.~~On average, an interquartile range (IQR) increase in XER was associated with a [Formula: see text] [95% confidence interval (CI): [Formula: see text], [Formula: see text]] decrease in BW and a [Formula: see text] (95% CI: 0.1, 0.5) decrease in birth length. Upon additional adjustment for GA, the estimated mean differences were [Formula: see text] (95% CI: [Formula: see text], 4) and [Formula: see text] (95% CI: [Formula: see text], 0.0), respectively.~~CONCLUSION: Higher-serum PFAA-induced xenoestrogenic activities were associated with lower BW and length in offspring, suggesting that PFAA mixtures may affect fetal growth by disrupting ER function.	●	●								-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
482	ヒト（生殖毒性）	Borghese, M. M.; Walker, M.; Helewa, M. E.; Fraser, W. D.; Arbuckle, T. E.	Association of perfluoroalkyl substances with gestational hypertension and preeclampsia in the MIREC study	2020	Environ Int. 2020 Aug;141:105789. doi: 10.1016/j.envint.2020.105789. Epub 2020 May 11.	Background: Perfluoroalkyl substances (PFAS) have been linked with a number of developmental, reproductive, hepatic, and cardiovascular health outcomes. However, the evidence for an association between PFAS and hypertensive disorders of pregnancy (including gestational hypertension and preeclampsia) is equivocal and warrants further investigation. Objectives: To examine the relationship between background levels of perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), and perfluorohexane sulfonate (PFHxS) and the development of gestational hypertension or preeclampsia in a Canadian pregnancy cohort. We also explored the potential for effect modification according to fetal sex. Methods: Maternal plasma samples were collected in the first trimester from participants in the MIREC study and were analyzed for PFOA, PFOS, and PFHxS. Blood pressure was measured during each trimester. Gestational hypertension and preeclampsia were defined using the Society of Obstetricians and Gynaecologists of Canada guidelines. Logistic regression models were used to derive adjusted odds ratios (OR) and 95% confidence intervals (CI) for associations between PFAS concentrations (per doubling of concentration as well as according to tertiles) and gestational hypertension or preeclampsia. Linear mixed models were used to examine the association between PFAS concentrations and changes in blood pressure throughout pregnancy. Results: Data from 1739 participants were analyzed. 90% of women were normotensive throughout pregnancy, 7% developed gestational hypertension without preeclampsia, and 3% developed preeclampsia. In the full analyses, neither PFOA nor PFOS were associated with gestational hypertension or preeclampsia. However, each doubling of PFHxS plasma concentration was associated with higher odds of developing preeclampsia (OR = 1.32; 95% CI: 1.03, 1.70). In addition, participants in the highest PFHxS tertile (1.4-40.0 μg/L) had higher odds of developing preeclampsia relative to those in the lowest tertile (OR = 3.06; 95% CI: 1.27, 7.39). In stratified analyses, this effect was only apparent among women carrying a female fetus (OR = 4.90; 95% CI: 1.02, 22.3). However, among women carrying a male fetus, both PFOS and PFHxS were associated with gestational hypertension, but not preeclampsia. Higher plasma concentrations of all three PFAS were associated with increases in diastolic blood pressure throughout pregnancy, and PFOA and PFHxS were also associated with systolic blood pressure. Discrepant findings were similarly revealed in analyses stratified by fetal sex. Conclusions: Higher levels of PFHxS were associated with the development of preeclampsia, but not gestational hypertension. Neither PFOA nor PFOS were associated with either outcome. However, we show, for the first time, that fetal sex may modify these associations, a finding which warrants replication and further study.	●	●							-	1	A	-
483	ヒト（発生毒性）	Braun, J. M.; Chen, A.; Romano, M. E.; Calafat, A. M.; Webster, G. M.; Yolton, K.; Lanphear, B. P.	Prenatal perfluoroalkyl substance exposure and child adiposity at 8 years of age: The HOME study	2016	Obesity (Silver Spring). 2016 Jan;24(1):231-7. doi: 10.1002/oby.21258. Epub 2015 Nov 11.	OBJECTIVE: To examine relationships between prenatal perfluoroalkyl substance (PFAS) exposure and adiposity in children born to women who lived downstream from a fluoropolymer manufacturing plant.METHODS: Data are from a prospective cohort in Cincinnati, Ohio (HOME Study). Perfluorooctanoic (PFOA), perfluorooctane sulfonic (PFOS), perfluorononanoic (PFNA), and perfluorohexane sulfonic (PFHxS) acids were measured in prenatal serum samples. Differences were measured in body mass index z-scores (BMI), waist circumference, and body fat at 8 years of age (n = 204) and BMI between 2-8 years of age (n = 285) according to PFAS concentrations.RESULTS: Children born to women in the top two PFOA terciles had greater adiposity at 8 years than children in the 1st tercile. For example, waist circumference (cm) was higher among children in the 2nd (4.3; 0.95% CI: 1.7, 6.9) and 3rd tercile (2.2; 0.95% CI: -0.5, 4.9) compared to children in the 1st tercile. Children in the top two PFOA terciles also had greater BMI gains from 2 to 8 years compared to children in the 1st tercile (P < 0.05). PFOS, PFNA, and PFHxS were not associated with adiposity.CONCLUSIONS: In this cohort, higher prenatal serum PFOA concentrations were associated with greater adiposity at 8 years and a more rapid increase in BMI between 2-8 years.	●	●	●	●					●	-		B	-
484	ヒト（発生毒性）	Braun, J. M.; Kalkbrenner, A. E.; Just, A. C.; Yolton, K.; Calafat, A. M.; Sjödin, A.; Hauser, R.; Webster, G. M.; Chen, A.; Lanphear, B. P.	Gestational exposure to endocrine-disrupting chemicals and reciprocal social, repetitive, and stereotypic behaviors in 4- and 5-year-old children: the HOME study	2014	Environ Health Perspect. 2014 May;122(5):513-20. doi: 10.1289/ehp.1307261. Epub 2014 Mar 12.	BACKGROUND: Endocrine-disrupting chemicals (EDCs) may be involved in the etiology of autism spectrum disorders, but identifying relevant chemicals within mixtures of EDCs is difficult.OBJECTIVE: Our goal was to identify gestational EDC exposures associated with autistic behaviors.METHODS: We measured the concentrations of 8 phthalate metabolites, bisphenol A, 25 polychlorinated biphenyls (PCBs), 6 organochlorine pesticides, 8 brominated flame retardants, and 4 perfluoroalkyl substances in blood or urine samples from 175 pregnant women in the HOME (Health Outcomes and Measures of the Environment) Study (Cincinnati, OH). When children were 4 and 5 years old, mothers completed the Social Responsiveness Scale (SRS), a measure of autistic behaviors. We examined confounder-adjusted associations between 52 EDCs and SRS scores using a two-stage hierarchical analysis to account for repeated measures and confounding by correlated EDCs.RESULTS: Most of the EDCs were associated with negligible absolute differences in SRS scores (≤ 1.5). Each 2-SD increase in serum concentrations of polybrominated diphenyl ether-28 (PBDE-28) (β = 2.5; 0.95 CI: -0.6, 5.6) or trans-nonachlor (β = 4.1; 0.95 CI: 0.8-7.3) was associated with more autistic behaviors. In contrast, fewer autistic behaviors were observed among children born to women with detectable versus nondetectable concentrations of PCB-178 (β = -3.0; 0.95 CI: -6.3, 0.2), β-hexachlorocyclohexane (β = -3.3; 0.95 CI: -6.1, -0.5), or PBDE-85 (β = -3.2; 0.95 CI: -5.9, -0.5). Increasing perfluorooctanoate (PFOA) concentrations were also associated with fewer autistic behaviors (β = -2.0; 0.95 CI: -4.4, 0.4).CONCLUSIONS: Some EDCs were associated with autistic behaviors in this cohort, but our modest sample size precludes us from dismissing chemicals with null associations. PFOA, β-hexachlorocyclohexane, PCB-178, PBDE-28, PBDE-85, and trans-nonachlor deserve additional scrutiny as factors that may be associated with childhood autistic behaviors.	●	●	●	●						-		B	-
485	ヒト（生殖毒性）	Buck Louis, G. M.; Chen, Z.; Schisterman, E. F.; Kim, S.; Sweeney, A. M.; Sundaram, R.; Lynch, C. D.; Gore-Langton, R. E.; Barr, D. B.	Perfluorochemicals and human semen quality: The LIFE Study	2015	Environ Health Perspect. 2015 Jan;123(1):57-63. doi: 10.1289/ehp.1307621. Epub 2014 Aug 15.	BACKGROUND: The relation between persistent environmental chemicals and semen quality is evolving, although limited data exist for men recruited from general populations.OBJECTIVES: We examined the relation between perfluorinated chemicals (PFCs) and semen quality among 501 male partners of couples planning pregnancy.METHODS: Using population-based sampling strategies, we recruited 501 couples discontinuing contraception from two U.S. geographic regions from 2005 through 2009 Baseline interviews and anthropometric assessments were conducted, followed by blood collection for the quantification of seven serum PFCs (perfluorosulfonates, perfluorocarboxylates, and perfluorosulfonamides) using tandem mass spectrometry. Men collected a baseline semen sample and another approximately 1 month later. Semen samples were shipped with freezer packs, and analyses were performed on the day after collection. We used linear regression to estimate the difference in each semen parameter associated with a one unit increase in the natural log-transformed PFC concentration after adjusting for confounders and modeling repeated semen samples. Sensitivity analyses included optimal Box-Cox transformation of semen quality end points.RESULTS: Six PFCs [2-(N-methyl-perfluorooctane sulfonamido) acetate (Me-PFOSA-AcOH), perfluorodecanoate (PFDeA), perfluorononanoate (PFNA), perfluorooctane sulfonamide (PFOSA), perfluorooctane sulfonate (PFOS), and perfluorooctanoic acid (PFOA)] were associated with 17 semen quality end points before Box-Cox transformation. PFOSA was associated with smaller sperm head area and perimeter, a lower percentage of DNA stainability, and a higher percentage of bicephalic and immature sperm. PFDeA, PFNA, PFOA, and PFOS were associated with a lower percentage of sperm with coiled tails.CONCLUSIONS: Select PFCs were associated with certain semen end points, with the most significant associations observed for PFOSA but with results in varying directions.	●	●		●					●	-		B	-
486	ヒト（生殖毒性）	Buck Louis, G. M.; Zhai, S.; Smarr, M. M.; Grewal, J.; Zhang, C.; Grantz, K. L.; Hinkle, S. N.; Sundaram, R.; Lee, S.; Honda, M.; Oh, J.; Kannan, K.	Endocrine disruptors and neonatal anthropometry, NICHD Fetal Growth Studies - Singletons	2018	Environ Int. 2018 Oct;119:515-526. doi: 10.1016/j.envint.2018.07.024. Epub 2018 Jul 26.	BACKGROUND: Intrauterine exposure to endocrine disrupting chemicals (EDCs) has been equivocally associated with birth weight, length and head circumference with limited attention to anthropometric endpoints such as umbilical circumference and limb lengths.OBJECTIVE: To explore 76 prenatal maternal plasma EDC concentrations in a healthy obstetric cohort and 7 neonatal anthropometric endpoints by maternal race/ethnicity.METHODS: The study cohort comprised 2106 (564 White, 549 Black, 590 Hispanic, 403 Asian) healthy pregnant women recruited from 12 U.S. clinical sites between 2009 and 2012 who were followed through delivery. Neonates underwent standardized anthropometric assessment (weight, length, head and umbilical circumference, and mid- upper arm and thigh length). Plasma EDC concentrations were quantified using high resolution gas chromatography-high resolution mass spectrometry and liquid chromatography-tandem mass spectrometry. EDCs were log-transformed and rescaled by their deviations (SD) when modeled relative to neonatal endpoints using linear regression adjusting for age, education, pre-pregnancy body mass index (BMI), serum cotinine, serum lipids for lipophilic chemicals, and a race/ethnicity interaction term; p-values had FALSE discovery rate correction (<0.05).RESULTS: The cohort comprised women aged 28 (SD = 5) years with normal BMIs (23.6 kg/m2, SD = 3). Maternal EDC concentrations varied by self-identified race/ethnicity and neonatal outcomes, though no specific EDC was consistently associated with neonatal anthropometric outcomes across racial/ethnic groups. For the overall cohort, perfluorooctanoic acid was negatively associated with birth length per SD increase in concentration (β = -0.23 cm; 0.95 CI -0.35, -0.10), while perfluorohexanesulfonic acid was negatively associated with umbilical circumference (β = -0.26 cm; 0.95 CI -0.40, -0.13), perfluorodecanoic acid with arm length (-0.09 cm; 0.95 CI -0.14, -0.04), and PCBs congeners 118/106 (-0.12 cm; 0.95 CI -0.20, -0.04) and 146/161 (-0.14 cm; 0.95 CI -0.23, -0.05) with thigh length, as were 7 other poly-and-perfluorinated alkyl substances (PFASs).CONCLUSIONS: Among healthy pregnant women with low risk antenatal profiles and relatively low EDC concentrations, reductions in umbilical circumference and bone lengths may be a sensitive marker of intrauterine EDC exposure, particularly for PFAS.	●	●	●							-	1	A	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ランク①	文献ランク②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
487	ヒト（発生毒性）	Callan, A. C.; Rotander, A.; Thompson, K.; Heyworth, J.; Mueller, J. F.; Odland, J. Ø.; Hinwood, A. L.	Maternal exposure to perfluoroalkyl acids measured in whole blood and birth outcomes in offspring	2016	Sci Total Environ. 2016 Nov 1;569-570:1107-1113. doi: 10.1016/j.scitotenv.2016.06.177. Epub 2016 Jul 4.	Perfluoralkyl and polyfluoralkyl substances have been measured in plasma and serum of pregnant women as a measure of prenatal exposure. Increased concentrations of individual perfluoroalkyl acids (PFAAs), (typically perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) have been reported to be associated with reductions in birth weight and other birth outcomes. We undertook a study of 14 PFAAs in whole blood (including PFOS, PFHxS, PFHpA, PFOA, PFNA, PFDA and PFUnDA) from 98 pregnant women in Western Australia from 2008 to 2011 Median concentrations (in μg/L) were: PFOS 1.99; PFHxS 0.33; PFOA 0.86; PFNA 0.30; PFDA 0.12 and PFUnDA 0.08. Infants born to women with the highest tertile of PFHxS exposure had an increased odds of being <95% of their optimal birth weight (OR 3.5, 0.95 CI 1.1-11.5). Conversely, maternal blood concentrations of PFUnDA were associated with non-significant increases in average birth weight (+102g, 0.95 CI -41, 245) and significant increases in proportion of optimal birth weight (+4.7%, 0.95 CI 0.7, 8.8) per ln-unit change. This study has reported a range of PFAAs in the whole blood of pregnant women and suggests that PFHxS and PFUnDA may influence foetal growth and warrant further attention. Additional studies are required to identify the sources of PFAA exposure with a view to prevention, in addition to further studies investigating the long term health effects of these ubiquitous chemicals.	●	●		●					-		B	-
488	ヒト（生殖毒性）	Campbell, S.; Raza, M.; Pollack, A. Z.	Perfluoroalkyl substances and endometriosis in US women in NHANES 2003-2006	2016	Reprod Toxicol. 2016 Oct;65:230-235. doi: 10.1016/j.reprotox.2016.08.009. Epub 2016 Aug 17.	Exposure to endocrine-active perfluoroalkyl substances (PFASs), is nearly ubiquitous, but data on the association between PFASs and endometriosis diagnosis are limited. We aimed to examine the relationship between PFASs and endometriosis. Women aged 20-50 years from the National Health and Nutrition Examination Survey (2003-2006) were selected (n=753). Serum PFAS levels were measured and endometriosis status was determined by self-report of doctor diagnosis. Weighted survey sampling logistic regression was used. Women reporting endometriosis were older (39.4 vs. 33.7 years), and more likely to be non-Hispanic white. Geometric mean levels of perfluorononanoic acid (PFNA), perfluorooctanoic acid (PFOA), and perfluorooctane sulfonate (PFOS) were significantly higher among women reporting endometriosis. Endometriosis was associated with select quartiles of PFOA, PFNA, and PFOS. Sensitivity analyses had similar results but wider confidence intervals. These findings suggest that PFOA, PFNA, and PFOS may be of interest in future studies with improved endometriosis diagnostic criteria and prospectively measured exposure.	●	●		●					-		B	-
489	ヒト（発生毒性）	Cao, W.; Liu, X.; Liu, X.; Zhou, Y.; Zhang, X.; Tian, H.; Wang, J.; Feng, S.; Wu, Y.; Bhatti, P.; Wen, S.; Sun, X.	Perfluoroalkyl substances in umbilical cord serum and gestational and postnatal growth in a Chinese birth cohort	2018	Environ Int. 2018 Jul;116:197-205. doi: 10.1016/j.envint.2018.04.015. Epub 2018 Apr 23.	Although animal studies have found that perfluoroalkyl substances (PFASs) affect gestational and postnatal growth, the epidemiological findings are limited and not in agreement. We explored the associations of PFAS concentrations in umbilical cord blood with gestational and postnatal growth in China. Three hundred thirty-seven singleton newborns and their mothers were recruited from November 2013 to December 2015 in Zhoukou City, China. Umbilical cord blood was collected to measure eleven PFASs by liquid chromatography-mass spectrometry. The index of gestational and postnatal growth contained fetal weight, length, and head circumference. These were obtained at birth and at the follow-up investigation (mean 19 months). Exposed to higher perfluorooctanoic acid (PFOA) were connected with reduced length at birth (p for trend = 0.01) and decreased postnatal weight (β = -429.2 g; 0.95 CI: -858.4, -0.121 for 2nd VS. 1st). Exposed to perfluoroundecanoic acid (PFUdA) were positively associated with indications of gestational growth and postnatal growth (p for trend = 0.02 for birth length; p for trend = 0.04 for postnatal length). Exposed to higher perfluorododecanoic acid (PFDoA) were associated with lower birth weight (β = -122.9 g, 0.95 CI: -244.7 to -1.2 for 2nd VS. 1st), but higher postnatal length (p for trend = 0.03). Neonates in the highest exposure group of per-fluorohexanesulfonate (PFHxS) showed decreased birth length (β = -0.33 cm, 0.95 CI: -0.68 to -0.01, for 2nd VS. 1st), but increased postnatal head circumference (p for trend = 0.04). Increased PFOA concentrations was associated with shorter birth length only in girls (p for trend = 0.04), suggesting that the effect of PFASs on gestational growth were different between boys and girls. In utero exposure to PFASs may affect gestational and postnatal growth.	●	●		●					-		B	-
490	ヒト（生殖毒性）	Caserta, D.; Ciardo, F.; Bordi, G.; Guerranti, C.; Fanello, E.; Perra, G.; Borghini, F.; La Rocca, C.; Tait, S.; Bergamasco, B.; Stecca, L.; Marci, R.; Lo Monte, G.; Soave, I.; Focardi, S.; Mantovani, A.; Moscarini, M.	Correlation of endocrine disrupting chemicals serum levels and white blood cells gene expression of nuclear receptors in a population of infertile women	2013	Int J Endocrinol. 2013;2013:510703. doi: 10.1155/2013/510703. Epub 2013 Apr 21.	Significant evidence supports that many endocrine disrupting chemicals could affect female reproductive health. Aim of this study was to compare the internal exposure to bisphenol A (BPA), perfluorooctane sulphonate (PFOS), perfluorooctanoic acid (PFOA), monoethylhexyl phthalate (MEHP), and di(2-ethylhexyl) phthalate (DEHP) in serum samples of 111 infertile women and 44 fertile women. Levels of gene expression of nuclear receptors (ER α , ER β , AR, AhR, PXR, and PPAR γ) were also analyzed as biomarkers of effective dose. The percentage of women with BPA concentrations above the limit of detection was significantly higher in infertile women than in controls. No statistically significant difference was found with regard to PFOS, PFOA, MEHP and DEHP. Infertile patients showed gene expression levels of ER α , ER β , AR, and PXR significantly higher than controls. In infertile women, a positive association was found between BPA and MEHP levels and ER α , ER β , AR, AhR, and PXR expression. PFOS concentration positively correlated with AR and PXR expression. PFOA levels negatively correlated with AhR expression. No correlation was found between DEHP levels and all evaluated nuclear receptors. This study underlines the need to provide special attention to substances that are still widely present in the environment and to integrate exposure measurements with relevant indicators of biological effects.	●	●							-		B	-
491	ヒト（発生毒性）	Chen, M. H.; Ha, E. H.; Liao, H. F.; Jeng, S. F.; Su, Y. N.; Wen, T. W.; Lien, G. W.; Chen, C. Y.; Hsieh, W. S.; Chen, P. C.	Perfluorinated compound levels in cord blood and neurodevelopment at 2 years of age	2013	Epidemiology. 2013 Nov;24(6):800-8. doi: 10.1097/EDE.0b013e3182a6dd46.	BACKGROUND: Epidemiologic data regarding the potential neurotoxicity of perfluorinated compounds (PFCs) are inconclusive. We investigated the associations between in utero exposure to perfluorooctanoic acid (PFOA) and perfluorooctyl sulfonate (PFOS) and early childhood neurodevelopment.METHODS: We recruited 239 mother-infant pairs in northern Taiwan from the Taiwan Birth Panel Study, which was established in 2004 We examined the association between PFCs in cord blood and children's neurodevelopment at 2 years of age, using the Comprehensive Developmental Inventory for Infants and Toddlers. This tool contains cognitive, language, motor, social, and self-help domains; test scores were further transformed into developmental quotients according to standardized norms. All multivariate regression models were adjusted for infant sex and gestational age, maternal education, family income, cord blood cotinine levels, postnatal environmental tobacco smoke exposure, and breastfeeding.RESULTS: Prenatal PFOS concentrations in both untransformed and natural log (Ln)-transformed values were associated with adverse performance on the whole test and the domains related to development. A dose-response relationship was observed when PFOS levels were categorized into four groups. This association was most obvious in relation to the gross-motor subdomain. Across the PFOS interquartile range, the quotients of the gross-motor subdomain decreased by 3.7 points (95% confidence interval [CI] = -6 to -1.5), with an increasing odds ratio of poor performance (2.4; 0.95 CI = 1.3 to 4.2). In contrast, measures of association between PFOA concentrations and test scores were close to null.CONCLUSIONS: Prenatal exposure to PFOS, but not PFOA, may affect children's development, especially gross-motor development at 2 years of age.	●	●		●					-		B	-
492	ヒト（発生毒性）	Christensen, K. Y.; Maisonet, M.; Rubin, C.; Holmes, A.; Calafat, A. M.; Kato, K.; Flanders, W. D.; Heron, J.; Mcgeehin, M. A.; Marcus, M.	Exposure to polyfluoroalkyl chemicals during pregnancy is not associated with offspring age at menarche in a contemporary British cohort	2011	Environ Int. 2011 Jan;37(1):129-35. doi: 10.1016/j.envint.2010.08.007. Epub 2010 Sep 16.	INTRODUCTION: Polyfluoroalkyl chemicals (PFCs) are commercially synthesized chemicals used in consumer products. Exposure to certain PFCs is widespread, and some PFCs may act as endocrine disruptors. We used data from the Avon Longitudinal Study of Parents and Children (ALSPAC) in the United Kingdom to conduct a nested case-control study examining the association between age at menarche, and exposure to PFCs during pregnancy.METHODS: Cases were selected from female offspring in the ALSPAC who reported menarche before the age of 11.5 years (n = 218), and controls were a random sample of remaining girls (n = 230). Serum samples taken from the girls' mothers during pregnancy (1991-1992) were analyzed using on-line solid-phase extraction coupled to isotope dilution high-performance liquid chromatography-tandem mass spectrometry for 8 PFCs. Logistic regression was used to determine association between maternal serum PFC concentrations, and odds of earlier age at menarche.RESULTS: PFOS and PFOA were the predominant PFCs (median serum concentrations of 19.8 ng/mL and 3.7 ng/mL). All but one PFC were detectable in most samples. Total PFC concentration varied by number of births (inverse association with birth order; p-value < 0.0001) and race of the child (higher among whites; p-value = 0.03). The serum concentrations of carboxylates were associated with increased odds of earlier age at menarche; concentrations of perfluorooctane sulfonamide, the sulfonamide esters and sulfonates were all associated with decreased odds of earlier age at menarche. However, all confidence intervals included the null value of 1.0.CONCLUSIONS: ALSPAC study participants had nearly ubiquitous exposure to most PFCs examined, but PFC exposure did not appear to be associated with altered age at menarche of their offspring.	●	●	●	●	●				-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報対象抽出	文献ランク①	文献ランク②
493	ヒト（生殖毒性）	Chu, C.; Zhou, Y.; Li, Q. Q.; Bloom, M. S.; Lin, S.; Yu, Y. J.; Chen, D.; Yu, H. Y.; Hu, L. W.; Yang, B. Y.; Zeng, X. W.; Dong, G. H.	Are perfluorooctane sulfonate alternatives safer? New insights from a birth cohort study	2020	Environ Int. 2020 Feb;135:105365. doi: 10.1016/j.envint.2019.105365. Epub 2019 Dec 9.	Background: Experimental studies show that chlorinated polyfluorinated ether sulfonic acids (Cl-PFESA 6:2 and 8:2), one of perfluoroalkyl substances (PFAS) used as perfluorooctane sulfonate (PFOS) alternatives, are reproductive toxicants in vivo and in vitro. However, the associations between gestational exposure to Cl-PFESAs and birth outcomes are unknown. Objectives: We investigated associations between 6:2 Cl-PFESA and 8:2 Cl-PFESA in maternal serum and birth outcomes. Methods: We measured four PFAS, including 6:2 Cl-PFESA, 8:2 Cl-PFESA, PFOS, and perfluorooctanoic acid (PFOA) in third-trimester maternal serum collected from 372 mother-child dyads participating in the Guangzhou Birth Cohort Study. Characteristics of mothers and infants were gathered from medical records and by interviewer-administered questionnaires. Results: PFOS was the most abundant PFAS in maternal serum (median: 7.15 ng/mL), followed by 6:2 Cl-PFESA (median: 2.41 ng/mL). Greater maternal serum levels of all PFAS alternatives were significantly associated with lower birth weight, adjusted for confounding variables. For example, each ln-ng/mL greater concentration of 6:2 Cl-PFESA and 8:2 Cl-PFESA was associated with a 54.44 g [95% confidence interval (CI): -95.66, -13.22] and 21.15 g (95% CI: -41.44, -0.86) lower birth weight, respectively. Greater continuous maternal serum 6:2 Cl-PFESA (OR: 2.67, 95% CI: 1.73, 4.15) and PFOS (OR: 2.03, 95% CI: 1.24, 3.32) were also associated with higher risks for preterm birth, adjusted for confounders, with a possible threshold effect at the highest quartile of 6:2 Cl-PFESA. Conclusions: For the first time, we report associations between maternal serum 6:2 Cl-PFESA and 8:2 Cl-PFESA concentrations and adverse birth outcomes. Our findings suggest that PFOS alternatives may be reproductive toxicants in human populations and should be considered with caution before widespread use. Given the preliminary nature of our results, additional epidemiological and toxicological investigations are needed to more definitively assess the risks.	●	●							●	-		C	-
494	ヒト（発生毒性）	Giovanni Costa 1, Samantha Sartori, Dario Consonni	Thirty years of medical surveillance in perfluooctanoic acid production workers	2019	Environ Int. 2019 Sep;130:104830. doi: 10.1016/j.envint.2019.05.024. Epub 2019 Jun 25.	BACKGROUND: Several studies have investigated the possible association between prenatal exposure to perfluoroalkyl substances (PFASs) and birth anthropometry. However, none has assessed fetal size longitudinally. We studied the possible association between PFASs and fetal biometry.METHODS: In 1230 mother-child pairs of three cohorts from the Spanish INMA-Project, we analyzed perfluorohexanesulfonic acid (PFHxS), perfluorooctanesulfonic acid (PFOS), perfluorooctanoic acid (PFOA), and perfluorononanoic acid (PFNA) in first-trimester maternal plasma (collection: 2003-2008). We measured abdominal circumference (AC), femur length (FL), biparietal diameter (BPD), and estimated fetal weight (EFW) by ultrasounds at 12, 20, and 34 gestational weeks. We conducted multivariable linear regression analyses between log2-transformed (PFASs) and SD-scores of fetal parameters in each cohort and subsequent meta-analysis. We also assessed effect modification by sex and maternal smoking.RESULTS: PFHxS, PFOA, PFOS, and PFNA medians were: 0.58, 2.35, 6.05, and 0.65 ng/mL, respectively. There were no associations for the whole population in any trimester of pregnancy. However, we found an indication that maternal smoking modified the effect in different directions depending on the PFAS. Among smokers (31%), we found negative associations between both PFOA and PFNA and FL or EFW at week 20 (% change ranging between -0.068 and -0.057 per twofold PFAS increase) and positive associations between PFHxS or PFOS and BPD at week 34 (6.8% and 6.3%, respectively).CONCLUSIONS: Results did not suggest an overall association between prenatal PFASs and fetal growth. The results among smokers should be taken with caution and further studies are warranted to elucidate the possible role of smoking in this association.	●									-		B	-
495	ヒト（生殖毒性）	Cui, Q.; Pan, Y.; Wang, J.; Liu, H.; Yao, B.; Dai, J.	Exposure to per- and polyfluoroalkyl substances (PFASs) in serum versus semen and their association with male reproductive hormones	2020	Environ Pollut. 2020 Nov;266(Pt 2):115330. doi: 10.1016/j.envpol.2020.115330. Epub 2020 Aug 6.	Given that per- and polyfluoroalkyl substances (PFASs) exhibit different distribution in the serum and semen of adult men, improving our understanding of the predictors of PFAS concentrations in paired serum and semen samples from an individual is essential. Here, we investigated and compared the effects of emerging and legacy PFAS concentrations in serum and semen on reproductive hormone levels in serum within a Chinese adult male population. We explored the relationships among perfluorooctanoate (PFOA), perfluorononanoate (PFNA), perfluorooctane sulfonate (PFOS), and chlorinated polyfluorinated ether sulfonate (6:2 Cl-PFESA) in serum and semen with reproductive hormones in serum among 651 adult men from Nanjing, China. Significant relationships among all analyzed serum and semen PFASs and decreased total testosterone (total T) were found. Serum and semen PFOA levels were associated with significant decreases in free T. Furthermore, the levels of sex hormone-binding globulin (SHBG) were significantly decreased in association with PFNA, PFOS, and 6:2 Cl-PFESA exposure. Negative relationships between the total T/luteinizing hormone (LH) ratio and semen concentrations of selected PFASs were also observed. After adjustment of PFAS concentrations (in both semen and serum), stronger associations of PFASs with total T, free T, estradiol (E2), SHBG, and total T/LH were observed in semen than in serum. We found that 84.8% of the associations between serum PFOA with total T were mediated by semen PFOA. Thus, elevated PFAS exposure may have negative effects on male reproductive health, and semen PFAS may be a better exposure indicator for the male reproductive system than serum PFAS.	●	●							●	-		B	-
496	ヒト（生殖毒性）	Darrow, L. A.; Stein, C. R.; Steenland, K.	Serum perfluorooctanoic acid and perfluorooctane sulfonate concentrations in relation to birth outcomes in the Mid-Ohio Valley, 2005-2010	2013	Environ Health Perspect. 2013 Oct;121(10):1207-13. doi: 10.1289/ehp.1206372. Epub 2013 Jul 9.	BACKGROUND: Previous research suggests perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) may be associated with adverse pregnancy outcomes.OBJECTIVE: We conducted a population-based study of PFOA and PFOS and birth outcomes from 2005 through 2010 in a Mid-Ohio Valley community exposed to high levels of PFOA through drinking-water contamination.METHODS: Women provided serum for PFOA and PFOS measurement in 2005-2006 and reported reproductive histories in subsequent follow-up interviews. Reported singleton live births among 1330 women after 1 January 2005 were linked to birth records (n = 1,630) to identify the outcomes of preterm birth (< 37 weeks gestation), pregnancy-induced hypertension, low birth weight (< 2500 g), and birth weight (grams) among full-term infants.RESULTS: We observed little or no evidence of association between maternal serum PFOA or PFOS and preterm birth (n = 158) or low birth weight (n = 88). Serum PFOA and PFOS were both positively associated with pregnancy-induced hypertension (n = 106), with adjusted odds ratios (ORs) per log unit increase in PFOA and PFOS of 1.27 (95% CI: 1.05, 1.55) and 1.47 (95% CI: 1.06, 2.04), respectively, but associations did not increase monotonically when categorized by quintiles. Results of subanalyses restricted to pregnancies conceived after blood collection were consistent with the main analyses. There was suggestion of a modest negative association between PFOS and birth weight in full-term infants (-29 g per log unit increase; 0.95 CI: -66, 7), which became stronger when restricted to births conceived after the blood sample collection (-49 g per log unit increase; 0.95 CI: -90, -8).CONCLUSION: Results provide some evidence of positive associations between measured serum perfluorinated compounds and pregnancy-induced hypertension and a negative association between PFOS and birth weight among full-term infants.	●	●		●			●		●	-		B	-
497	ヒト（発生毒性）	de Cock, M.; de Boer, M. R.; Lamoree, M.; Legler, J.; van De Bor, M.	First Year Growth in Relation to Prenatal Exposure to Endocrine Disruptors - A Dutch Prospective Cohort Study	2014	Int J Environ Res Public Health. 2014 Jul 10;11(7):7001-21. doi: 10.3390/ijerph110707001.	Growth in the first year of life may already be predictive of obesity later in childhood. The objective was to assess the association between prenatal exposure to various endocrine disrupting chemicals (EDCs) and child growth during the first year. Dichloro-diphenyldichloroethylene (DDE), mono(2-ethyl-5-carboxypentyl)phthalate (MECPP), mono(2-ethyl-5-hydroxyhexyl)phthalate (MEHHP), mono(2-ethyl-5-oxohexyl)phthalate (MEOHP), polychlorinated biphenyl-153, perfluorooctanesulfonic acid, and perfluorooctanoic acid were measured in cord plasma or breast milk. Data on weight, length, and head circumference (HC) until 11 months after birth was obtained from 89 mother-child pairs. Mixed models were composed for each health outcome and exposure in quartiles. For MEOHP, boys in quartile 1 had a higher BMI than higher exposed boys (p = 0.029). High DDE exposure was associated with low BMI over time in boys (0.8 kg/m(2) difference at 11 m). Boys with high MECPP exposure had a greater HC (1.0 cm difference at 11 m) than other boys (p = 0.047), as did girls in the second quartile of MEHHP (p = 0.018) and DDE (p < 0.001) exposure. In conclusion, exposure to phthalates and DDE was associated with BMI as well as with HC during the first year after birth. These results should be interpreted with caution though, due to the	●	●		●						-		C	-
498	ヒト（発生毒性）	de Cock, M.; de Boer, M. R.; Lamoree, M.; Legler, J.; van de Bor, M.	Prenatal exposure to endocrine disrupting chemicals in relation to thyroid hormone levels in infants - a Dutch prospective cohort study	2014	Environ Health. 2014 Dec 10;13:106. doi: 10.1186/1476-069X-13-106.	BACKGROUND: Endocrine disrupting chemicals (EDCs) present in the environment may disrupt thyroid hormones, which in early life are essential for brain development. Observational studies regarding this topic are still limited, however as the presence of chemicals in the environment is ubiquitous, further research is warranted. The objective of the current study was to assess the association between exposure markers of various EDCs and thyroxine (T4) levels in newborns in a mother-child cohort in the Netherlands.METHODS: Exposure to dichlorodiphenyldichloroethylene (DDE), three di-2-ethylhexyl phthalate (DEHP) metabolites, hexachlorobenzene (HCB), polychlorinated biphenyl (PCB)-153, perfluorooctanesulfonic acid (PFOS), and perfluorooctanoic acid (PFOA) was determined in cord plasma or breast milk, and information on T4 levels in heel prick blood spots was obtained through the neonatal screening programme in the Netherlands. Linear regression models were composed to determine associations between each of the compounds and T4, which were stratified for gender and adjusted for a priori defined covariates.RESULTS: Mean T4 level was 86.9 nmol/L (n = 83). Girls in the highest quartile of DDE and PFOA exposure showed an increased T4 level compared to the lowest quartile with both crude and fully adjusted models (DDE > 107.5 ng/L, 24.8 nmol/L, 0.95 CI 0.79, 48.75; PFOA > 1200 ng/L, 38.6 nmol/L, 0.95 CI 13.34, 63.83). In boys a lower T4 level was seen in the second quartile of exposure for both PFOS and PFOA, however after fully adjusting the models these associations were attenuated. No effects were observed for the other compounds.CONCLUSION: DDE and perfluorinated alkyl acids may be associated with T4 in a sex-specific manner. These results should however be interpreted with caution, due to the relatively small study population. More research is warranted, as studies on the role of environmental contaminants in this area are still limited.	●	●								-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
499	ヒト（発生毒性）	de Cock, M.; De Boer, M. R.; Lamoree, M.; Legler, J.; Van De Bor, M.	Prenatal exposure to endocrine disrupting chemicals and birth weight-A prospective cohort study	2016	J Environ Sci Health A Tox Hazard Subst Environ Eng. 2016 Jan 28;51(2):178-185. doi: 10.1080/10934529.2015.1087753. Epub 2015 Nov 25.	Prenatal exposure to endocrine disrupting chemicals may affect fetal development through disruption of hormonal actions and epigenetic modifications, potentially predisposing individuals to later on-set health risks, such as obesity. The objective of this study was to determine associations between biological exposure markers of various endocrine disrupting chemicals and birth weight in a newly established, prospective mother-child cohort in the Netherlands. Birth weight (n = 91) was obtained from birth records, and exposure to dichlorodiphenyldichloroethylene (DDE), three di-2-ethylhexyl phthalate (DEHP) metabolites, polychlorinated biphenyl-153, perfluorooctanesulfonic acid (PFOS), and perfluorooctanoic acid (PFOA) was determined in cord plasma. For DDE, exposure was also measured in breast milk. Linear regression analysis was used to determine associations between compounds and birth weight, which were stratified for gender and adjusted for a priori defined covariates. Increased exposure to DDE was associated with lower birth weight in boys (>95.89 ng L(-1), -325.9 g, 0.95 CI -634.26 to -17.56), whereas in girls a tendency towards a higher birth weight was observed. Lower birth weights for boys were also observed for high exposure to MECPP, and to a certain extent also for PFOA. MEHHP and PFOS exposure on the other hand were associated with higher birth weights in boys. In girls no effects were observed for these compounds. It can be concluded that prenatal exposure to DDE, perfluorinated alkyl acids, and phthalates was associated with changes in birth weight in this population. Associations were gender specific, and appeared to be non-linear. Since the population was relatively small, results should be interpreted with caution.	●	●					●		-		B	-
500	ヒト（生殖毒性）	Dhingra, R.; Winquist, A.; Darrow, L. A.; Klein, M.; Steenland, K.	Perfluorooctanoic acid exposure and natural menopause: A longitudinal study in a community cohort	2016	Environ Res. 2016 Apr;146:323-30. doi: 10.1016/j.envres.2015.12.037. Epub 2016 Jan 21.	BACKGROUND: Impaired kidney function and earlier menopause were associated with perfluorooctanoic acid (PFOA) serum levels in previous cross-sectional studies. Reverse causation, whereby health outcomes increase serum PFOA, may underlie these associations.OBJECTIVE: We compared measured (subject to reverse causation) versus modeled (unaffected by reverse causation) serum PFOA in association with these outcomes to examine the possible role of reverse causation in these associations.METHODS: In cross-sectional analyses, we analyzed PFOA in relation to self-reported menopause among women (n = 9,192) 30-65 years old and in relation to kidney function among adults > 20 years old (n = 29,499) in a highly exposed Mid-Ohio Valley cohort. Estimated glomerular filtration rate (eGFR, a marker of kidney function) and serum PFOA concentration were measured in blood samples collected during 2005-2006. Retrospective year-specific serum PFOA estimates were modeled independently of measured PFOA based on residential history and plant emissions. Using measured and modeled PFOA in 2005 or 2006 (predictor variables), cross-sectional associations were assessed for eGFR and menopause (yes/no). We also analyzed measured PFOA (dependent variable) in relation to the number of years since menopause.RESULTS: Menopause and eGFR were significantly associated with measured (trend tests: p = 0.013, p =0.0005, respectively) but not with modeled serum PFOA (p = 0.50, p = 0.76, respectively). Measured PFOA levels increased for the first 7 years after menopause (trend test, p < 0.0001), providing further evidence that the observed association between measured PFOA and menopause is subject to reverse causation for this outcome.CONCLUSION: Our results support the conjecture that in previous studies, earlier menopause and reduced kidney function are the causes rather than the results of increased measured serum PFOA. These results suggest caution in using biomarkers in cross-sectional studies. Citation: Dhingra R, Winquist A, Darrow LA, Klein M, Steenland K. 2017 A study of reverse causation: examining the associations of perfluorooctanoic acid serum levels with two outcomes.	●	●		●						-		B	-
501	ヒト（生殖毒性）	Ding, N.; Harlow, S. D.; Randolph, J. F.; Calafat, A. M.; Mukherjee, B.; Batterman, S.; Gold, E. B.; Park, S. K.	Associations of perfluoroalkyl substances with incident natural menopause: The study of women's health across the nation	2020	J Clin Endocrinol Metab. 2020 Sep 1;105(9):e3169-e3182. doi: 10.1210/clinem/dgaa303.	Context: Previous epidemiologic studies of per- and polyfluoroalkyl substances (PFASs) and menopausal timing conducted in cross-sectional settings were limited by reverse causation because PFAS serum concentrations increase after menopause. Objectives: To investigate associations between perfluoroalkyl substances and incident natural menopause. Design and setting: A prospective cohort of midlife women, the Study of Women's Health Across the Nation, 1999-2017. Participants: 1120 multiracial/ethnic premenopausal women aged 45-56 years. Methods: Serum concentrations of perfluoroalkyls were quantified by high-performance liquid chromatography isotope dilution tandem mass spectrometry. Natural menopause was defined as the bleeding episode prior to at least 12 months of amenorrhea not due to surgery or hormone use. Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). Results: Participants contributed 5466 person-years of follow-up, and 578 had incident natural menopause. Compared with the lowest tertile, women at the highest tertile of baseline serum concentrations had adjusted HR for natural menopause of 1.26 (95% CI: 1.02-1.57) for n-perfluorooctane sulfonic acid (n-PFOS) (Ptrend = .03), 1.27 (95% CI: 1.01-1.59) for branched-PFOS (Ptrend = .03), and 1.31 (95% CI: 1.04-1.65) for n-perfluorooctanoic acid (Ptrend = .01). Women were classified into four clusters based on their overall PFAS concentrations as mixtures: low, low-medium, medium-high, and high. Compared with the low cluster, the high cluster had a HR of 1.63 (95% CI: 1.08-2.45), which is equivalent to 2.0 years earlier median time to natural menopause. Conclusion: This study suggests that select PFAS serum concentrations are associated with earlier natural menopause, a risk factor for adverse health outcomes in later life.	●	●								-		B	-
502	ヒト（生殖毒性）	Donley, G. M.; Taylor, E.; Jeddy, Z.; Namulanda, G.; Hartman, T. J.	Association between in utero perfluoroalkyl substance exposure and anti-Müllerian hormone levels in adolescent females in a British cohort	2019	Environ Res. 2019 Oct;177:108585. doi: 10.1016/j.envres.2019.108585. Epub 2019 Jul 18.	Evidence indicates that in utero environmental exposures could influence reproduction in female offspring. Perfluoroalkyl substances (PFAS) are synthetic, ubiquitous endocrine disrupting chemicals that can cross the placental barrier. Lower levels of anti-Müllerian hormone (AMH), a biomarker of ovarian reserve, are associated with reduced fertility. We investigated the association between in utero PFAS exposure and AMH levels in female adolescents using data from the Avon Longitudinal Study of Parents and Children, a British pregnancy cohort recruited between 1991 and 1992 Maternal serum samples were collected during pregnancy and analyzed for concentrations of commonly found PFAS-perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), perfluorohexane sulfonate (PFHxS), and perfluorononanoic acid (PFNA). AMH levels were measured in serum of female offspring (mean age, 15.4 years) and log-transformed for analyses. We used a sample of 446 mother-daughter dyads for multivariable linear regression analyses, controlling for maternal age at delivery, pre-pregnancy body-mass index, and maternal education. Multiple imputation was utilized to impute missing values of AMH -0.612 and covariates. Median PFAS concentrations (ng/mL) were as follows: PFOS 19.8 (IQR:15.1, 24.9), PFOA 3.7 (IQR: 2.8, 4.8), PFHxS 1.6 (IQR: 1.2, 2.2), PFNA 0.5 (IQR: 0.4, 0.7). The geometric mean AMH concentration was 3.9 ng/mL (95% CI: 3.8, 4.0). After controlling for confounders, mean differences in AMH per one ng/mL higher PFOA, PFOS, PFHxS, and PFNA were 0.036 (95% CI: 1.4%, 8.6%), 0.007 (95% CI: 0.2%, 1.5%), 0.009 (95% CI: 0.4%, 2.2%), and 0.12 (95% CI: 42.8%, 66.8%) respectively. These findings suggest there is no association between in utero PFAS exposure and AMH levels in female adolescents.	●	●								-		B	-
503	ヒト（生殖毒性）	Dreyer, A. F.; Jensen, R. C.; Glintborg, D.; Schmedes, A. V.; Brandslund, I.; Nielsen, F.; Kyhl, H. B.; Jensen, T. K.; Andersen, M. S.	Perfluoroalkyl substance exposure early in pregnancy was negatively associated with late pregnancy cortisone levels	2020	J Clin Endocrinol Metab. 2020 Aug 1;105(8):dgaa292. doi: 10.1210/clinem/dgaa292.	Introduction During pregnancy, maternal cortisol levels are increased 3-fold by the third trimester. The enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD, isoforms 1 and 2) regulates the balance between cortisol and cortisone levels. Perfluoroalkyl substances (PFAS) have been reported to inhibit 11β-HSD1 and more potently 11β-HSD2, which could lead to reduced levels of cortisol and more extensively cortisone. Aim The aim of this work is to investigate a possible effect of early pregnancy PFAS exposure on late pregnancy activity of 11β-HSD1 and 11β-HSD2 assessed by cortisol and cortisone levels in diurnal urine (dU) and blood samples. Methods This study is part of the prospective cohort study, Odense Child Cohort (OCC). A total of 1628 pregnant women had serum (S) concentrations of 5 PFAS (perfluorooctanoic acid [PFOA], perfluorooctane sulfonic acid [PFOS], perfluorohexane sulfonic acid [PFHxS], perfluorononanoic acid [PFNA], and perfluorodecanoic acid (PFDA)) measured in the first trimester (median gestational week, GW 11). dU cortisol and cortisone (n = 344) and S-cortisol (n = 1048) were measured in the third trimester (median GW 27). Results In multiple regression analyses, a 2-fold increase in S-PFOS was significantly associated with lower dU-cortisone (β = –9.1%, P < .05) and higher dU-cortisol/dU-cortisone (dU-C/C) (β = 9.3%, P < .05). In crude models, a doubling in PFOS, PFOA, PFHxS, and PFNA concentrations were associated with a significant increase in S-cortisol; however, these associations became insignificant after adjustment. Conclusion Early pregnancy maternal S-PFAS were inversely associated with late pregnancy dU-cortisone, indicating reduced activity of 11β-HSD2.	●	●								-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献ランク①	文献ランク②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
504	ヒト（発生毒性）	Dzierlenga, M.,.W.; Crawford, L.,.,; Longnecker, M.,.P.	Birth weight and perfluorooctane sulfonic acid: a random-effects meta-regression analysis	2020	Environ Epidemiol. 2020 Apr 23;4(3):e095. doi: 10.1097/EE9.0000000000000095. eCollection 2020 Jun.	Background: Perfluorooctane sulfonic acid (PFOS) is a ubiquitous environmental contaminant. Most people in developed countries have detectable serum concentrations. Lower birth weight has been associated with serum PFOS in studies world-wide, many of which have been published only recently. Methods: To facilitate a causal assessment of the birth weight and PFOS association, we updated previous meta-analyses of the association and employed a method that facilitated inclusion of all available data in one analysis. Our analysis was based on observations from 29 studies. Results: The random effects summary was －3.22 g/ng/ml (95% confidence interval [CI] = －5.11, －1.33). In a subgroup analysis stratified by when in pregnancy the PFOS concentration was measured, the summary for the early group was －1.35 (95% CI = －2.33, －0.37) and for the later group was －7.17 (95% CI = －10.93, －3.41). In a meta-regression model including a term for timing of blood draw, the intercept was slightly positive but essentially zero (0.59 g/ng/ml, 95% CI = －1.94, 3.11). In other words, the model indicated that when blood was drawn at the very beginning of pregnancy, there was essentially no relation of birth weight to PFOS. The results from the subgroup analyses differed from those from the model because the average gestational age at blood draw in the early group was 14 weeks, when bias would still be expected. A stronger inverse association in Asian studies was not completely explained by their blood draws being from later in pregnancy. Conclusions: The evidence was weakly or not supportive of a causal association.	●	●								-		B	-
505	ヒト（発生毒性）	Fei, C.; Mclaughlin, J. K.; Lipworth, L.; Olsen, J.	Prenatal exposure to perfluorooctanoate (PFOA) and perfluorooctanesulfonate (PFOS) and maternally reported developmental milestones in infancy	2008	Environ Health Perspect. 2008 Oct;116(10):1391-5. doi: 10.1289/ehp.11277. Epub 2008 Jun 4.	BACKGROUND: Perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) are fluorinated organic compounds present in the general population at low concentrations. Animal studies have shown that they may affect neuromuscular development at high concentrations.OBJECTIVES: We investigated the association between plasma levels of PFOS and PFOA in pregnant women and motor and mental developmental milestones of their children.METHODS: We randomly selected 1400 pairs of pregnant women and their children from the Danish National Birth Cohort. PFOS and PFOA were measured in maternal blood samples taken in early pregnancy. Apgar score was abstracted from the National Hospital Discharge Register in Denmark. Developmental milestones were reported by mothers using highly structured questionnaires when the children were around 6 months and 18 months of age.RESULTS: Mothers who had higher levels of PFOA and PFOS gave birth to children who had similar Apgar scores and reached virtually all of the development milestones at the same time as children born to mothers with lower exposure levels. Children who were born to mothers with higher PFOS levels were slightly more likely to start sitting without support at a later age.CONCLUSION: We found no convincing associations between developmental milestones in early childhood and levels of PFOA or PFOS as measured in maternal plasma early in pregnancy.	●	●		●	●	●				-		B	-
506	ヒト（生殖毒性）	Fei, Chunyuan; McLaughlin, Joseph K; Tarone, Robert E; Olsen, Jørn	Perfluorinated chemicals and fetal growth: A study within the Danish National Birth Cohort	2007	Environ Health Perspect. 2007 Nov;115(11):1677-82. doi: 10.1289/ehp.10506.	BACKGROUND: Perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) are man-made, persistent organic pollutants widely spread throughout the environment and human populations. They have been found to interfere with fetal growth in some animal models, but whether a similar effect is seen in humans is uncertain. OBJECTIVES: We investigated the association between plasma levels of PFOS and PFOA in pregnant women and their infants' birth weight and length of gestation. METHODS: We randomly selected 1,400 women and their infants from the Danish National Birth Cohort among those who completed all four computer-assisted telephone interviews, provided the first blood samples between gestational weeks 4 and 14, and who gave birth to a single live-born child without congenital malformation. PFOS and PFOA were measured by high performance liquid chromatography-tandem mass spectrometer. RESULTS: PFOS and PFOA levels in maternal plasma were on average 35.3 and 5.6 ng/mL, respectively. Only PFOA levels were inversely associated with birth weight (adjusted beta = -10.63 g; 95% confidence interval, -20.79 to -0.47 g). Neither maternal PFOS nor PFOA levels were consistently associated with the risk for preterm birth or low birth weight. We observed no adverse effects for maternal PFOS or PFOA levels on small for gestational age. CONCLUSION: Our nationwide cohort data suggest an inverse association between maternal plasma PFOA levels and birth weight. Because of widespread exposure to these chemicals, our findings may be of potential public health concern.	●	●	●	●			●			-		B	-
507	ヒト（発生毒性）	Fei, C.; Olsen, J.	Prenatal exposure to perfluorinated chemicals and behavioral or coordination problems at age 7 years	2011	Environ Health Perspect. 2011 Apr;119(4):573-8. doi: 10.1289/ehp.1002026. Epub 2010 Nov 9.	Potential neurotoxic effects of perfluorinated compounds (PFCs) have been reported in highly exposed animals, but whether these chemicals are neurotoxic in humans is not known. We therefore investigated whether prenatal exposure to perfluorooctanoic acid (PFOA) or perfluorooctane sulfate (PFOS), two of the most prevalent PFCs, are associated with behavioral or coordination problems in early childhood. We used data from the Danish National Birth Cohort, which enrolled mothers in early pregnancy, and we measured maternal blood levels of PFOA and PFOS using specimens drawn around 8 weeks of gestation. When the children reached 7 years of age, mothers completed the Strengths and Difficulties Questionnaire (SDQ, n=787) and the Developmental Coordination Disorder Questionnaire (DCDQ, n=526) to assess behavioral health and motor coordination of their children. SDQ scores above the 90th percentile were a priori defined to identify behavioral problems and DCDQ scores below the 10th percentile were defined as a potential DCD. The median concentrations of PFOS and PFOA in maternal blood were 34.4 ng/mL [interquartile range (IQR), 26.6-44.5] and 5.4 ng/mL (IQR, 4.0-7.1), respectively, similar to distributions reported for populations without occupational exposure. We found no association between higher SDQ scores and maternal levels of PFOS or PFOA, nor did we see any statistically significant association with motor coordination disorders. The findings suggest that background levels of PFOA and PFOS are not associated with behavioral and motor coordination problems in childhood. However, effects on other developmental end points, including cognitive, attentional, and clinical mental disorders not measured in this study, cannot be ruled out.	●	●		●	●	●				-		B	-
508	ヒト（生殖毒性）	Fei, C. Y.; Mclaughlin, J. K.; Lipworth, L.; Olsen, J.	Maternal levels of perfluorinated chemicals and subfecundity	2009	Hum Reprod. 2009 May;24(5):1200-5. doi: 10.1093/humrep/den490. Epub 2009 Jan 28.	Background: Perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) are ubiquitous man-made compounds that are possible hormonal disruptors. We examined whether exposure to these compounds may decrease fecundity in humans. Methods: Plasma levels of PFOS and PFOA were measured at weeks 4-14 of pregnancy among 1240 women from the Danish National Birth Cohort recruited from 1996 to 2002. For this pregnancy, women reported time to pregnancy (TTP) in five categories (<1, 1-2, 3-5, 6-12 and >12 months). Infertility was defined as having a TTP of >12 months or received infertility treatment to establish this pregnancy. Results: Longer TTP was associated with higher maternal levels of PFOA and PFOS (P < 0.001). Compared with women in the lowest exposure quartile, the adjusted odds of infertility increased by 70-134 and 60-154% among women in the higher three quartiles of PFOS and PFOA, respectively. Fecundity odds ratios (FORs) were also estimated using Cox discrete-time models. The adjusted FORs were virtually identical for women in the three highest exposure groups of PFOS (FOR = 0.70, 0.67 and 0.74, respectively) compared with the lowest quartile. A linear-like trend was observed for PFOA (FOR = 0.72, 0.73 and 0.60 for three highest quartiles versus lowest quartile). When all quartiles were included in a likelihood ratio test, the trends were significant for PFOS and PFOA (P = 0.002 and P < 0.001, respectively). Conclusions: These findings suggest that PFOA and PFOS exposure at plasma levels seen in the general population may reduce fecundity; such exposure levels are common in developed countries.	●	●		●	●	●			●	-		B	-
509	ヒト（発生毒性）	Forns, J.; Iszatt, N.; White, R. A.; Mandal, S.; Sabaredzovic, A.; Lamoree, M.; Thomsen, C.; Haug, L. S.; Stigum, H.; Eggesbø, M.	Perfluoroalkyl substances measured in breast milk and child neuropsychological development in a Norwegian birth cohort study	2015	Environ Int. 2015 Oct;83:176-82. doi: 10.1016/j.envint.2015.06.013. Epub 2015 Jul 6.	Perfluoroalkyl substances (PFASs) are chemicals with potential neurotoxic effects although the current evidence is still limited. This study investigated the association between perinatal exposure to perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) and neuropsychological development assessed at 6, 12 and 24 months. We measured PFOS and PFOA in breast milk samples collected one month after delivery by mothers of children participating in the HUMIS study (Norway). Cognitive and psychomotor development was measured at 6 and at 24 months using the Ages and Stages Questionnaire (ASQ-II). Behavioral development was assessed using the infant-toddler symptom checklist (ITSC) at 12 and at 24 months. Weighted logistic regression and weighted negative binomial regression models were applied to analyze the associations between PFASs and ASQ-II and ITSC, respectively. The median concentration of PFOS was 110 ng/L, while the median for PFOA was 40 ng/L. We did not detect an increased risk of having an abnormal score in ASQ-II at 6 months or 24 months. Moreover, no consistent increase in behavioral problems assessed at 12 and 24 months by ITSC questionnaire was detected. We observed no association between perinatal PFOS and PFOA exposure and early neuropsychological development. Further longitudinal studies are needed to confirm the effects of these compounds on neuropsychological development in older children.	●	●		●						-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献①ラン	文献②ラン
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
510	ヒト（発生毒性）	Gao, K.,e; Zhuang, T.; Liu, X.; Fu, J.; Zhang, J.; Fu, J.,ie; Wang, L.; Zhang, A.; Liang, Y.; Song, M.; Jiang, G.	Prenatal Exposure to Per- and Polyfluoroalkyl Substances (PFASs) and Association between the Placental Transfer Efficiencies and Dissociation Constant of Serum Proteins-PFAS Complexes	2019	Environ Sci Technol. 2019 Jun 4;53(11):6529-6538. doi: 10.1021/acs.est.9b00715. Epub 2019 May 23.	Information on placental transfer and adverse outcomes of short-chain per- and polyfluoroalkyl substance (PFASs) is limited, and factors responsible for PFAS placental transfer are still unclear. In the present study, concentrations of 21 PFASs were analyzed in 132 paired maternal and cord serum samples collected from residents in Beijing, China, and the placental transfer efficiency (PTE) of each PFAS was calculated. PTEs of short-chain perfluoroalkyl acids (PFAAs), including PFBA (146%), PFBS (97%), PFPeA (118%), and PFHxA (110%), were first reported, and a complete U-shaped trend of PTEs from C4 to C13 of perfluoroalkyl carboxylic acids (PFCAs) was obtained. Positive association between maternal weight and PTE of perfluorooctanesulfonate (PFOS) (p < 0.05) and negative association between maternal PFBA concentration and birth length (p < 0.01) were observed. Using in vitro experiments, we further determined equilibrium dissociation constants (Kds) of human serum albumin (HSA)-PFAS complexes (Kd-HP), serum proteins-PFAS complexes (Kd-SP), and liver-fatty acid binding protein (L-FABP)-PFAS complexes (Kd-LP) and found that they were all significantly correlated with PTEs of PFASs. The correlation coefficient was 0.92, 0.89, and 0.86, respectively (p < 0.01 in all three tests), suggesting that Kds of protein (serum)-PFAS complexes can play an important role in trans-placental transfer of PFASs in human and Kd-HP plays a pivotal role.	●	●							-	1	A	-
511	ヒト（生殖毒性）	Goudarzi, H.; Araki, A.; Itoh, S.; Sasaki, S.; Miyashita, C.; Mitsui, T.; Nakazawa, H.; Nonomura, K.; Kishi, R.	The association of prenatal exposure to perfluorinated chemicals with glucocorticoid and androgenic hormones in cord blood samples: The Hokkaido study	2017	Environ Health Perspect. 2017 Jan;125(1):111-118. doi: 10.1289/EHP142. Epub 2016 May 24.	Background: Perfluorinated chemicals (PFCs) disrupt cholesterol homeostasis. All steroid hormones are derived from cholesterol, and steroid hormones such as glucocorticoids and androgenic hormones mediate several vital physiologic functions. However, the in utero effects of PFCs exposure on the homeostasis of these steroid hormones are not well understood in humans. Objectives: We examined the relationship between prenatal exposure to perfluorooctane sulfonate (PFOS)/perfluorooctanoate (PFOA) and cord blood levels of glucocorticoid and androgenic hormones. Methods: We conducted a hospital-based birth cohort study between July 2002 and October 2005 in Sapporo, Japan (n = 514). In total, 185 mother-infant pairs were included in the present study. Prenatal PFOS and PFOA levels in maternal serum samples were measured using liquid chromatography-tandem mass spectrometry (LC-MS-MS). Cord blood levels of glucocorticoid (cortisol and cortisone) and androgenic hormones [dehydroepiandrosterone (DHEA) and androstenedione] were also measured in the same way. Results: We found a dose-response relationship of prenatal PFOS, but not PFOA, exposure with glucocorticoid levels after adjusting for potential confounders. Cortisol and cortisone concentrations were -23.98-ng/mL (95% CI: -0.47.12, -11.99; p for trend = 0.006) and -63.21-ng/mL (95% CI: -132.56, -26.72; p for trend < 0.001) lower, respectively, in infants with prenatal PFOS exposure in the fourth quartile compared with those in the first quartile. The highest quartile of prenatal PFOS exposure was positively associated with a 1.33-ng/mL higher DHEA level compared with the lowest quartile (95% CI: 0.17, 1.82; p for trend = 0.017), whereas PFOA showed a negative association with DHEA levels (quartile 4 vs. quartile 1: -1.23 ng/mL, 95% CI: -1.72, -0.25; p for trend = 0.004). We observed no significant association between PFCs and androstenedione levels. Conclusions: Our results indicate that prenatal exposure to PFCs is significantly associated with glucocorticoid and DHEA levels in cord blood. Citation: Goudarzi H, Araki A, Itoh S, Sasaki S, Miyashita C, Mitsui T, Nakazawa H, Nonomura K, Kishi R. 2017. The association of prenatal exposure to perfluorinated chemicals with glucocorticoid and androgenic hormones in cord blood samples: the Hokkaido Study.	●	●							-		B	-
512	ヒト（発生毒性）	Goudarzi, H.; Nakajima, S.; Ikeno, T.; Sasaki, S.; Kobayashi, S.; Miyashita, C.; Ito, S.; Araki, A.; Nakazawa, H.; Kishi, R.	Prenatal exposure to perfluorinated chemicals and neurodevelopment in early infancy: The Hokkaido Study	2016	Sci Total Environ. 2016 Jan 15;541:1002-1010. doi: 10.1016/j.scitotenv.2015.10.017. Epub 2015 Nov 11.	Perfluorinated chemicals (PFCs) are ubiquitous and persistent pollutants widely detected in blood samples of animals and humans across the globe. Although animal studies have shown the potential neurotoxicity of PFCs, there are few epidemiological studies regarding neurological effects of PFCs in humans, and those studies have had inconclusive results. In this study, we conducted a hospital-based prospective birth cohort study between 2002 and 2005 (n=514) to examine the associations between prenatal perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) exposures and the neurodevelopment of infants at 6 (n=173) and 18 (n=133) months of age. Using the second edition of the Bayley Scales of Infant Development (BSID II), the Mental and Psychomotor Developmental Indices (MDI and PDI, respectively) were assessed. PFOS and PFOA were measured in maternal serum samples by liquid chromatography-tandem mass spectrometry. After controlling for confounders, prenatal PFOA concentrations were associated with the MDI of female (but not male) infants at 6 months of age (β=-0.296; 0.95 confidence interval (CI): -11.96, -0.682). Furthermore, females born to mothers with prenatal concentrations of PFOA in the fourth quartile had MDI scores -5.05 (95% CI: -10.66 to 0.55) lower than females born to mothers with concentrations of PFOA in the first quartile (p for trend=0.045). However, PFOA concentrations were not significantly associated with neurodevelopmental indices at 18 months of age. In addition, we did not observe any significant association between PFOS concentrations and neurodevelopmental outcomes in early infancy. In conclusion, our results suggest that prenatal PFOA exposure may affect female mental scales of neurodevelopment at 6 months of age. Further studies with larger sample sizes and longer observation periods are required to clarify sex difference of the neurodevelopmental effects.	●	●		●					-		B	-
513	ヒト（生殖毒性）	Govarts, Eva; Iszatt, Nina; Trnovec, Tomas; de Cock, Marijke; Eggesbø, Merete; Palkovicova Murinova, Lubica; van de Bor, Margot; Guxens, Mònica; Chevrier, Cécile; Koppen, Gudrun; Lamoree, Marja; Hertz-Picciotto, Irva; Lopez-Espinosa, Maria-Jose; Lertxundi, Aitana; Grimalt, Joan O; Torrent, Maties; Goñi-Irigoyen, Fernando; Vermeulen, Roel; Legler, Juliette; Schoeters, Greet	Prenatal exposure to endocrine disrupting chemicals and risk of being born small for gestational age: Pooled analysis of seven European birth cohorts	2018	Environ Int. 2018 Jun;115:267-278. doi: 10.1016/j.envint.2018.03.017. Epub 2018 Mar 30.	BACKGROUND AND AIMS: There is evidence that endocrine disrupting chemicals (EDCs) have developmental effects at environmental concentrations. We investigated whether some EDCs are associated with the adverse birth outcome Small for Gestational Age (SGA). METHODS: We used PCB 153, p,p'-DDE, HCB, PFOS and PFOA measured in maternal, cord blood or breast milk samples of 5446 mother-child pairs (subset of 693 for the perfluorinated compounds) from seven European birth cohorts (1997-2012). SGA infants were those with birth weight below the 10th percentile for the norms defined by gestational age, country and infant's sex. We modelled the association between measured or estimated cord serum EDC concentrations and SGA using multiple logistic regression analyses. We explored effect modification by child's sex and maternal smoking during pregnancy. RESULTS: Among the 5446 newborns, 570 (10.5%) were SGA. An interquartile range (IQR) increase in PCB 153 was associated with a modestly increased risk of SGA (odds ratio (OR) of 1.05 [95% CI: 1.04-1.07]) that was stronger in girls (OR of 1.09 [95% CI: 1.04-1.14]) than in boys (OR of 1.03 [95% CI: 1.03-1.04]) (p-interaction = 0.025). For HCB, we found a modestly increased odds of SGA in girls (OR of 1.04 [95% CI: 1.01-1.07] per IQR increase), and an inverse association in boys (OR of 0.90 [95% CI: 0.85-0.95]) (p-interaction = 0.0003). Assessment of the HCB-sex-smoking interaction suggested that the increased odds of SGA associated with HCB exposure was only in girls of smoking mothers (OR of 1.18 [95% CI: 1.11-1.25]) (p-interaction = 0.055). Higher concentrations of PFOA were associated with greater risk of SGA (OR of 1.64 [95% CI: 0.97-2.76]). Elevated PFOS levels were associated with increased odds of SGA in newborns of mothers who smoked during pregnancy (OR of 1.63 [95% CI: 1.02-2.59]), while an inverse association was found in those of non-smoking mothers (OR of 0.66 [95% CI: 0.61-0.72]) (p-interaction = 0.0004). No significant associations were found for p,p'-DDE. CONCLUSIONS: Prenatal environmental exposure to organochlorine and perfluorinated compounds with endocrine disrupting properties may contribute to the prevalence of SGA. We found indication of effect modification by child's sex and smoking during pregnancy. The direction of the associations differed by chemical and these effect modifiers, suggesting diverse mechanisms of action and biological pathways.	●	●	●	●					-		B	-
514	ヒト（発生毒性）	Govarts, E; Remy, S; Bruckers, L; Den Hond, E; Sioen, I; Nelen, V; Baeyens, W; Nawrot, TS; Loots, I; Van Larebeke, N; Schoeters, G.	Combined effects of prenatal exposures to environmental chemicals on birth weight	2016	Int J Environ Res Public Health. 2016 May 12;13(5):495. doi: 10.3390/ijerph13050495.	Prenatal chemical exposure has been frequently associated with reduced fetal growth by single pollutant regression models although inconsistent results have been obtained. Our study estimated the effects of exposure to single pollutants and mixtures on birth weight in 248 mother-child pairs. Arsenic, copper, lead, manganese and thallium were measured in cord blood, cadmium in maternal blood, methylmercury in maternal hair, and five organochlorines, two perfluorinated compounds and diethylhexyl phthalate metabolites in cord plasma. Daily exposure to particulate matter was modeled and averaged over the duration of gestation. In single pollutant models, arsenic was significantly associated with reduced birth weight. The effect estimate increased when including cadmium, and mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP) co-exposure. Combining exposures by principal component analysis generated an exposure factor loaded by cadmium and arsenic that was associated with reduced birth weight. MECPP induced gender specific effects. In girls, the effect estimate was doubled with co-exposure of thallium, PFOS, lead, cadmium, manganese, and mercury, while in boys, the mixture of MECPP with cadmium showed the strongest association with birth weight. In conclusion, birth weight was consistently inversely associated with exposure to pollutant mixtures. Chemicals not showing significant associations at single pollutant level contributed to stronger effects when analyzed as mixtures.	●	●		●					-		B	-
515	ヒト（発生毒性）	Gyllenhammar, I.; Diderholm, B.; Gustafsson, J.; Berger, U.; Ridefelt, P.; Benskin, J. P.; Lignell, S.; Lampa, E.; Glynn, A.	Perfluoroalkyl acid levels in first-time mothers in relation to offspring weight gain and growth	2018	Environ Int. 2018 Feb;111:191-199. doi: 10.1016/j.envint.2017.12.002. Epub 2017 Dec 20.	We investigated if maternal body burdens of perfluoroalkyl acids (PFAAs) at the time of delivery are associated with birth outcome and if early life exposure (in utero/nursing) is associated with early childhood growth and weight gain. Maternal PFAA body burdens were estimated by analysis of serum samples from mothers living in Uppsala County, Sweden (POPUP), sampled three weeks after delivery between 1996 and 2011 Data on child length and weight were collected from medical records and converted into standard deviation scores (SDS). Multiple linear regression models with appropriate covariates were used to analyze associations between maternal PFAA levels and birth outcomes (n=381). After birth Generalized Least Squares models were used to analyze associations between maternal PFAA and child growth (n=200). Inverse associations were found between maternal levels of perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), and perfluoroundecanoic acid (PFUnDA), and birth weight SDS with a change of -0.1 to -0.18 weight SDS for an inter-quartile range (IQR) increase in ng/g PFAA. After birth, weight and length SDS were not significantly associated with maternal PFAA. However, BMI SDS was significantly associated with PFOA, PFNA, and PFHxS at 3 and 4years of age, and with PFOS at 4 and 5years of age. If causal, these associations suggest that PFAA affects fetal and childhood body development in different directions.	●	●							-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①抽出	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
516	ヒト（発生毒性）	Hack, M; Klein, N K; Taylor, H G	Long-term developmental outcomes of low birth weight infants	1995	Future Child. 1995 Spring;5(1):176-96. doi: 10.2307/1602514	Advances in neonatal medicine have resulted in the increased survival of infants at lower and lower birth weight. While these medical success stories highlight the power of medical technology to save many of the tiniest infants at birth, serious questions remain about how these infants will develop and whether they will have normal, productive lives. Low birth weight children can be born at term or before term and have varying degrees of social and medical risk. Because low birth weight children are not a homogeneous group, they have a broad spectrum of growth, health, and developmental outcomes. While the vast majority of low birth weight children have normal outcomes, as a group they generally have higher rates of subnormal growth, illnesses, and neurodevelopmental problems. These problems increase as the child's birth weight decreases. With the exception of a small minority of low birth weight children with mental retardation and/or cerebral palsy, the developmental sequelae for most low birth weight infants include mild problems in cognition, attention, and neuromotor functioning. Long-term follow-up studies conducted on children born in the 1960s indicated that the adverse consequences of being born low birth weight were still apparent in adolescence. Adverse sociodemographic factors negatively affect developmental outcomes across the continuum of low birth weight and appear to have far greater effects on long-term cognitive outcomes than most of the biological risk factors. In addition, the cognitive defects associated with social or environmental risks become more pronounced as the child ages. Enrichment programs for low birth weight children seem to be most effective for the moderately low birth weight child who comes from a lower socioeconomic group. Continued research and attempts to decrease the rate of low birth weight and associated perinatal medical sequelae are of primary importance. Ongoing documentation of the long-term outcome of low birth weight children needs to be mandated, as does the implementation of environmental enrichment programs to help ameliorate the long-term consequences for infants who are born low birth weight.	●	●								-		D	-
517	ヒト（発生毒性）	Hartman, T. J.; Calafat, A. M.; Holmes, A. K.; Marcus, M.; Northstone, K.; Flanders, W. D.; Kato, K.; Taylor, E. V.	Prenatal exposure to perfluoroalkyl substances and body fatness in girls	2017	Child Obes. 2017 Jun;13(3):222-230. doi: 10.1089/chi.2016.0126. Epub 2017 Jan 27.	BACKGROUND: Perfluoroalkyl substances (PFASs) are used in surface coatings that resist stains, grease, and water.METHODS: The association between in utero PFAS exposure and girls' body fatness at age 9 was analyzed in The Avon Longitudinal Study of Parents and Children (UK). Maternal serum [median 15 weeks: interquartile range (IQR) 10 and 28 weeks of gestation] was analyzed for perfluorooctane sulfonate (PFOS), perfluorooctanoate (PFOA), perfluorohexane sulfonate (PFHxS), and perfluorononanoate (PFNA). Body composition was measured by dual X-ray emission absorptiometry, and percent total body fat (%BF) was calculated. Associations between PFASs and body fatness were modeled by multivariable linear regression.RESULTS: Among 359 girls, median (IQR) %BF was 27.5 (IQR 21.7-34.6). Median (IQR) concentrations (all ng/mL) were 3.7 (2.9-4.8) for PFOA, 19.8 (15.0-25.3) for PFOS, 1.6 (1.3-2.2) for PFHxS, and 0.5 (0.4-0.7) for PFNA. Maternal PFAS concentrations were not significantly associated with daughters' total %BF overall. Mothers' educational status modified associations for PFOA and PFOS with %BF (P-interactions: 0.005 and 0.02, respectively). %BF was higher [1.4%; 0.95 confidence interval (95% CI): 0.3 to 2.5] for each one unit (ng/mL) higher PFOA among girls with mothers in the middle education group, but lower (-0.6%; 0.95 CI: -1.12 to -0.04) for the corresponding comparison among girls with mothers with the highest education. %BF was lower (-0.2%; 0.95 CI: -0.3 to -0.1) for each one unit higher PFOS among girls with the most educated mothers.CONCLUSIONS: Prenatal exposure to PFOA and PFOS was associated with girls' %BF within some strata of maternal education status. PFHxS and PFNA were not associated with %BF.	●	●	●	●						-		B	-
518	ヒト（発生毒性）	Hjermitslev, M. H.; Long, M.; Wielsøe, M.; Bonefeld-Jørgensen, E. C.	Persistent organic pollutants in Greenlandic pregnant women and indices of foetal growth: The ACCEPT study	2019	Sci Total Environ. 2020 Jan 1;698:134118. doi: 10.1016/j.scitotenv.2019.134118. Epub 2019 Aug 27.	The Greenlandic population has some of the highest levels of environmental persistent organic pollutants (POPs) globally. Studies have previously found POPs to be linked with disturbance of child development, immune function and reproductive abilities. We investigated the associations between serum POP levels of pregnant women in Greenland and their infant's birth weight, length, head circumference and gestational age (GA) at birth. Pregnant Greenlandic women (n = 504) were enrolled during pregnancy and serum levels of the lipophilic POPs (Organochlorine pesticides, Polychlorinated biphenyls and Polybrominated diphenyl ethers) and the amphiphilic POPs, Perfluoroalkylated substances (PFASs), were measured. We analysed the associations between maternal serum levels of POPs and birth weight, length, head circumference and GA using linear regression analysis. We found significant inverse associations between Perfluorooctanoic Acid (PFOA) and birth weight (adjusted β = -119 g, 0.95 CI: -201; -36), birth length (adjusted β = -0.37 cm, 0.95 CI: -0.76; 0.02, borderline significant) and head circumference (adjusted β = -0.35 cm, 0.95 CI: -0.59; -0.10) and a positive association with GA (adjusted β = 0.45 week, 0.95 CI: 0.17; 0.74). For the lipophilic POPs, we found an overall trend of inverse associations to foetal growth indices. In conclusion, we found that the amphiphilic PFOA had a significant inversely association with foetal growth indices, whereas GA was positively associated. The data indicate that POPs have a negative effect on foetal growth.	●	●								-		B	-
519	ヒト（発生毒性）	Hoffman, K.; Webster, T. F.; Weisskopf, M. G.; Weinberg, J.; Vieira, V. M.	Exposure to polyfluoroalkyl chemicals and attention deficit/hyperactivity disorder in U.S. Children 12–15 Years of Age	2010	Environ Health Perspect. 2010 Dec;118(12):1762-7. doi: 10.1289/ehp.1001898. Epub 2010 Jun 15.	BACKGROUND: Polyfluoroalkyl chemicals (PFCs) have been widely used in consumer products. Exposures in the United States and in world populations are widespread. PFC exposures have been linked to various health impacts, and data in animals suggest that PFCs may be potential developmental neurotoxicants.OBJECTIVES: We evaluated the associations between exposures to four PFCs and parental report of diagnosis of attention deficit/hyperactivity disorder (ADHD).METHODS: Data were obtained from the National Health and Nutrition Examination Survey (NHANES) 1999-2000 and 2003-2004 for children 12-15 years of age. Parental report of a previous diagnosis by a doctor or health care professional of ADHD in the child was the primary outcome measure. Perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), and perfluorohexane sulfonic acid (PFHxS) levels were measured in serum samples from each child.RESULTS: Parents reported that 48 of 571 children included in the analysis had been diagnosed with ADHD. The adjusted odds ratio (OR) for parentally reported ADHD in association with a 1-μg/L increase in serum PFOS (modeled as a continuous predictor) was 1.03 [95% confidence interval (CI), 1.01-1.05]. Adjusted ORs for 1-μg/L increases in PFOA and PFHxS were also statistically significant (PFOA: OR = 1.12; 0.95 CI, 1.01-1.23; PFHxS: OR = 1.06; 0.95 CI, 1.02-1.11), and we observed a nonsignificant positive association with PFNA (OR = 1.32; 0.95 CI, 0.86-2.02).CONCLUSIONS: Our results, using cross-sectional data, are consistent with increased odds of ADHD in children with higher serum PFC levels. Given the extremely prevalent exposure to PFCs, follow-up of these data with cohort studies is needed.	●	●		●	●	●				-		B	-
520	ヒト（発生毒性）	Høyer, B. B.; Ramlau-Hansen, C. H.; Obel, C.; Pedersen, H. S.; Hernik, A.; Ogniev, V.; Jönsson, B. A.; Lindh, C. H.; Rylander, L.; Rignell-Hydbom, A.; Bonde, J. P.; Toft, G.	Pregnancy serum concentrations of perfluorinated alkyl substances and offspring behaviour and motor development at age 5-9 years--a prospective study	2015	Environ Health. 2015 Jan 7;14:2. doi: 10.1186/1476-069X-14-2.	BACKGROUND: In animal studies, perfluorinated alkyl substances affect growth and neuro-behavioural outcomes. Human epidemiological studies are sparse. The aim was to investigate the association between pregnancy serum concentrations of perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) and offspring behaviour and motor development at 44690 years of age.METHODS: Maternal sera from the INUENDO cohort (2002-2004) comprising 1106 mother-child pairs from Greenland, Kharkiv (Ukraine) and Warsaw (Poland) were analysed for PFOS and PFOA, using liquid-chromatography-tandem-mass-spectrometry. Exposures were grouped into country specific as well as pooled tertiles as well as being used as continuous variables for statistical analyses. Child motor development and behaviour at follow-up (2010-2012) were measured by the Developmental Coordination Disorder Questionnaire 2007 (DCDQ) and Strength and Difficulties Questionnaire (SDQ), respectively. Exposure-outcome associations were analysed by multiple logistic and linear regression analyses.RESULTS: In the pooled analysis, odds ratio (OR) (95% confidence interval (CI)) for hyperactivity was 3.1 (1.3, 7.2) comparing children prenatally exposed to the highest PFOA tertile with those exposed to the lowest PFOA tertile. Comparing children in the highest PFOS tertile with those in the lowest PFOS tertile showed elevated but statistically non-significant OR of hyperactivity (OR (95% CI) 1.7 (0.9, 3.2)). In Greenland, elevated PFOS was associated with higher SDQ-total scores indicating more behavioural problems (β (95% CI)=1.0 (0.1, 2.0)) and elevated PFOA was associated with higher hyperactivity sub-scale scores indicating more hyperactive behaviour (β (95% CI)=0.5 (0.1, 0.9)). Prenatal PFOS and PFOA exposures were not associated with motor difficulties.CONCLUSIONS: Prenatal exposure to PFOS and PFOA may have a small to moderate effect on children's neuro-behavioural development, specifically in terms of hyperactive behaviour. The associations were strongest in Greenland where exposure contrast is largest.	●	●		●						-		B	-
521	ヒト（発生毒性）	Hu, Q.; Franklin, J. N.; Bryan, I.; Morris, E.; Wood, A.; Dewitt, J. C.	Does developmental exposure to perfluorooctanoic acid (PFOA) induce immunopathologies commonly observed in neurodevelopmental disorders? Neurotoxicology 33: 1491-1498	2012	Neurotoxicology. 2012 Dec;33(6):1491-1498. doi: 10.1016/j.neuro.2012.10.016. Epub 2012 Nov 5.	Immune comorbidities often are reported in subsets of patients with neurodevelopmental disorders, including autism spectrum disorders and attention-deficit hyperactivity disorder. A common immunopathology is an increase in serum autoantibodies against myelin basic protein (MBP) relative to control patients. Increases in autoantibodies suggest possible deficits in self-tolerance that may contribute to the formation of brain-specific autoantibodies and subsequent effects on the central nervous system (CNS). Oppositely, the formation of neuronal autoantibodies may be a reaction to neuronal injury or damage. Perfluorooctanoic acid (PFOA) is an environmental pollutant that induces multisystem toxicity in rodent models, including immunotoxicity and neurotoxicity. We hypothesized that developmental exposure to PFOA may induce immunotoxicity similar to that observed in subsets of patients with neurodevelopmental disorders. To test this hypothesis, we evaluated subsets of T cells from spleens, serum markers of autoreactivity, and levels of MBP and T cell infiltration in the cerebella of adult offspring exposed to 0.02, 0.2, or 2mg/kg of PFOA given to dams from gestation through lactation. Litter weights of offspring from dams exposed to 2mg/kg of PFOA were reduced by 32.6%, on average, from postnatal day one (PND1) through weaning (PND21). The percentage of splenic CD4+CD25+Foxp3+ T cells in male and female offspring from dams exposed to 2mg/kg of PFOA was reduced by 0.22 relative to the control percentage. Ex vivo co-cultures of splenic CD4+CD25+ T cells and CD4+CD25- T cells from dosed male offspring produced less IL-10 relative to control cells. Anti-ssDNA, a serum marker of autoreactivity, was decreased by 26%, on average, in female offspring from dams exposed to 0.02 and 2mg/kg PFOA. No other endpoints were statistically different by dose. These data suggest that developmental PFOA exposure may impact T cell responses and may be a possible route to downstream effects on other systems.	●	●								-		C	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ラン①抽出	文献ラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
522	ヒト（発生毒性）	Huang, R.; Chen, Q.; Zhang, L.; Luo, K.; Chen, L.; Zhao, S.; Feng, L.; Zhang, J.	Association between polyfluoroalkyl chemical concentrations and leucocyte telomere length in US adults	2019	Sci Total Environ. 2019 Feb 25;653:547-553. doi: 10.1016/j.scitotenv.2018.10.400. Epub 2018 Oct 30.	Exposure to some environmental chemicals is reportedly associated with the leucocyte telomere length (LTL), but the effects of the non-occupational exposure to polyfluoroalkyl chemical (PFCs) on the LTL are not well understood. Using data from 773 participants in the National Health and Nutrition Examination Survey (NHANES) conducted in 1999-2000, we analysed the association between blood PFC concentrations and LTL. Coefficients (betas) and 95% confidence intervals (CIs) for the blood PFC concentrations in association with the LTL were estimated using multivariate linear regression models after adjustment for age, gender, race, body mass index (BMI), poverty income ratio, educational level, white blood cell count, C-reactive protein and other PFCs. The results identified a strong positive association between the blood perfluorooctane sulfonic acid (PFOS) concentration and LTL in adults, and no associations were found between the LTL and other PFCs. In the linear regression models, each increment of one standard deviation (SD) in the base-10-logarithm-transformed PFOS concentration was associated with a 21-bp increase in the LTL in the fully adjusted model (P = 0.033). Moreover, serum PFOS was associated with the LTL mainly in females and individuals aged 40-50, as demonstrated by stratified analyses. These results provide epidemiological evidence showing that environment-related levels of serum PFOS are positively associated with the LTL in adults.	●	●							-		B	-
523	ヒト（発生毒性）	Huo, Xiaona; Huang, Rong; Gan, Yuexin; Luo, Kai; Aimuzi, Ruxianguli; Nian, Min; Ao, Junjie; Feng, Liping; Tian, Ying; Wang, Weiye; Ye, Weiping; Zhang, Jun	Perfluoroalkyl substances in early pregnancy and risk of hypertensive disorders of pregnancy: A prospective cohort study	2020	Environ Int. 2020 May;138:105656. doi: 10.1016/j.envint.2020.105656. Epub 2020 Mar 27.	BACKGROUND: Perfluoroalkyl substances (PFASs) were reported to be associated with hypertensive disorders of pregnancy (HDP) but the results were inconsistent and prospective data are scarce. We aimed to examine these associations in a large prospective birth cohort study in Shanghai, China. METHODS: A total of 10 PFASs were measured by high-performance liquid chromatography/tandem mass spectrometry (HPLC/MS-MS) in the plasma samples from 3220 women who were enrolled during early pregnancy and gave birth to a singleton live birth between 2013 and 2016. The outcomes included gestational hypertension (GH), preeclampsia (PE) and overall HDP. Associations of these outcomes with each PFASs were estimated by multivariable logistic regression and expressed as odd ratios (ORs) and 95% confidence intervals (95% CIs). Potential non-linear association between PFASs and HDP was examined with restricted cubic spline model. To handle the potential confounding by correlated PFASs, we applied elastic net regression (ENR) to identify independent PFASs components of outcomes. RESULTS: Among all singleton live births, the incidence rates of GH and PE were 2.0% and 2.2%, respectively. Overall, PFASs did not show a significant and consistent pattern of the associations with GH, PE or overall HDP, both before and after controlling for potential confounders. ENR model confirmed the results that there was no independently predictive role of PFASs on GH, PE or overall HDP. CONCLUSIONS: In this large prospective cohort study, maternal plasma concentration of PFASs in early pregnancy were not associated with GH, PE or overall HDP in singleton livebirths.	●	●							-		B	-
524	ヒト（発生毒性）	Huo, X.; Zhang, L.; Huang, R.; Feng, L.; Wang, W.; Zhang, J.; Shanghai Birth Cohort	Perfluoroalkyl substances exposure in early pregnancy and preterm birth in singleton pregnancies: a prospective cohort study	2020	Environ Health. 2020 Jun 3;19(1):60. doi: 10.1186/s12940-020-00616-8.	BACKGROUND: Preterm birth (PTB, < 37 completed weeks' gestation) is one of the global public health concerns. Epidemiologic evidence on the potential impact of perfluoroalkyl substances (PFAS) on PTB is still limited and inconsistent. We aimed to investigate the associations between prenatal PFAS exposure and PTB among singleton live births.METHODS: We studied 2849 mother-infant pairs in the Shanghai Birth Cohort (SBC) from 2013 to 2016 Ten PFAS in maternal plasma in early pregnancy (gestational age, median (interquartile range): 15 (13-16) weeks) were measured. Primary outcomes were duration of gestation, PTB, spontaneous PTB and clinically indicated PTB. A linear regression model was used to assess the associations between ln-transformed PFAS and duration of gestation (in weeks). Logistic regression models were applied to estimate the relative risks of these outcomes.RESULTS: The incidence of overall PTB was 0.048 (95% confidence limit: 4.0-5.6%, n = 136) in this study population. In the linear regression analyses, PFAS were not associated with the duration of gestation after controlling for potential confounders. In the multiple logistic models, no significant associations were observed between PFAS and overall PTB, spontaneous or indicated PTB.CONCLUSION: In this prospective cohort study, we did not observe significant associations between maternal plasma PFAS concentrations in early pregnancy and gestational length, overall PTB, spontaneous or indicated PTB.	●	●							-		B	-
525	ヒト（発生毒性）	Hurley, S.; Goldberg, D.; Wang, M.; Park, J. S.; Petreas, M.; Bernstein, L.; Anton-Culver, H.; Nelson, D. O.; Reynolds, P.	Breast cancer risk and serum levels of per- and poly-fluoroalkyl substances: a case-control study nested in the California Teachers Study	2018	Environ Health. 2018 Nov 27;17(1):83. doi: 10.1186/s12940-018-0426-6.	BACKGROUND: Per- and poly- fluoroalkyl substances (PFASs) are a large family of synthetic chemicals, some of which are mammary toxicants and endocrine disruptors. Their potential as breast carcinogens is unclear. Our objective was to evaluate the risk of breast cancer associated with serum PFAS concentrations in a nested case-control study within the California Teachers Study.METHODS: Participants were 902 women with invasive breast cancer (cases) and 858 with no such diagnosis (controls) who provided 10 mL of blood and were interviewed during 2011-2015, an average of 35 months after case diagnosis. PFASs were measured using automated online SPE-HPLC-MS/MS methods. Statistical analyses were restricted to six PFASs with detection frequencies ≥ 95%: PFOA (Perfluorooctanoic acid), PFNA (Perfluorononanoic acid), PFUnDA (Perfluoroundecanoic acid), PFHxS (Perfluorohexane sulfonic acid), PFOS (Perfluorooctane sulfonic acid), and MeFOSAA (2-(N-Methyl-perfluorooctane sulfonamido) acetic acid. Unconditional logistic regression was used to calculate adjusted odds ratios (ORs), estimating the breast cancer risk associated with each PFAS.RESULTS: For all cases of invasive breast cancer, none of the adjusted ORs were statistically significant but marginally significant ORs < 1.0 were observed for PFUnDA and PFHxS (p-trend = 0.08). Adjusted ORs < 1.0 for PFUnDA and PFHxS were statistically significant (p ≤ 0.05) among the 107 cases with hormone-negative tumors but not the 743 with hormone-positive tumors.CONCLUSION: Overall, these findings do not provide evidence that serum PFAS levels measured after diagnosis are related to breast cancer risk. The few inverse associations found may be due to chance or may be artifacts of study design. Future studies should incorporate information about genetic susceptibility, endogenous estrogen levels, and measurements of PFASs prior to diagnosis and treatment.	●	●							-		B	-
526	ヒト（発生毒性）	Itoh, S.; Araki, A.; Mitsui, T.; Miyashita, C.; Goudarzi, H.; Sasaki, S.; Cho, K.; Nakazawa, H.; Iwasaki, Y.; Shinohara, N.; Nonomura, K.; Kishi, R.	Association of perfluoroalkyl substances exposure in utero with reproductive hormone levels in cord blood in the Hokkaido Study on Environment and Children's Health	2016	Environ Int. 2016 Sep;94:51-59. doi: 10.1016/j.envint.2016.05.011. Epub 2016 May 19.	BACKGROUND: Exposure to perfluoroalkyl substances (PFASs) may disrupt reproductive function in animals and humans. Although PFASs can cross the human placental barrier, few studies evaluated the effects of prenatal PFAS exposure on the fetus' reproductive hormones.OBJECTIVE: To explore the associations of prenatal exposure to perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) with cord blood reproductive hormones.METHODS: In the prospective birth cohort (Sapporo cohort of the Hokkaido study), we included 189 mother-infant pairs recruited in 2002-2005 with both prenatal maternal and cord blood samples. PFOS and PFOA levels in maternal blood after the second trimester were measured via liquid chromatography-tandem mass spectrometry. We also measured cord blood levels of the fetuses' reproductive hormones, including estradiol (E2), total testosterone (T), progesterone (P4), inhibin B, insulin-like factor 3, steroid hormone binding globulin, follicle-stimulating hormone, and luteinizing hormone, and prolactin (PRL).RESULTS: The median PFOS and PFOA levels in maternal serum were 5.2ng/mL and 1.4ng/mL, respectively. In the fully adjusted linear regression analyses of the male infants, maternal PFOS levels were significantly associated with E2 and positively, and T/E2, P4, and inhibin B inversely; PFOA levels were positively associated with inhibin B levels. Among the female infants, there were significant inverse associations between PFOS levels and P4 and PRL levels, although there were no significant associations between PFOA levels and the female infants' reproductive hormone levels.CONCLUSIONS: These results suggest that the fetal synthesis and secretion of reproductive hormones may be affected by in utero exposure to measurable levels of PFOS and PFOA.	●	●		●					-		B	-
527	ヒト（発生毒性）	Jeddy, Z.; Hartman, T. J.; Taylor, E. V.; Poteete, C.; Kordas, K.	Prenatal concentrations of perfluoroalkyl substances and early communication development in British girls	2017	Early Hum Dev. 2017 Jun;109:15-20. doi: 10.1016/j.earlhumdev.2017.04.004. Epub 2017 Apr 12.	Perfluoroalkyl substances (PFAS), found in many household products and classed as endocrine disrupting chemicals, can be transferred through the placenta and are associated with multiple developmental deficits in offspring. Using data from the Avon Longitudinal Study of Parents and Children (ALSPAC), we investigated the association between intrauterine exposure to PFAS and early communication development in 432 mother-daughter dyads at 15 and 38months of age. Concentrations of perfluorooctane sulfonate (PFOS), perfluorooctanoate (PFOA), perfluorohexane sulfonate (PFHxS), and perfluorononanoate (PFNA) were measured in maternal serum collected during pregnancy. Early communication development was measured with the ALSPAC-adapted MacArthur Communicative Development Inventories for Infants and Toddlers. The infant questionnaire measured verbal comprehension, vocabulary comprehension and production, nonverbal communication, and social development. The toddler questionnaire measured language, intelligibility, and communicative sub-scores. Multivariable linear regression was used to examine associations between each PFAS exposure and each communication sub-scale score. The association between maternal PFAS concentrations and early communication development at 15 and 38months of age varied by maternal age at delivery. In daughters of younger mothers (<25years of age), every 1ng/mL of PFOS was associated with a 3.82 point (95% confidence interval (CI): -6.18, -1.47) lower vocabulary score at 15months and a 0.8 point (95% CI: -1.74, 0.14) lower language score at 38months. Prenatal exposure to select PFAS was positively and negatively associated with communication development among girls, with inconsistent pattern of association across all measured PFAS and endpoints.	●	●		●					-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報対象抽出	文献クラン①	文献クラン②
528	ヒト（発生毒性）	Jensen, R. C.; Andersen, M. S.; Larsen, P. V.; Glintborg, D.; Dalgård, C.; Timmermann, C. A. G.; Nielsen, F.; Sandberg, M. B.; Andersen, H. R.; Christesen, H. T.; Grandjean, P.; Jensen, T. K.	Prenatal Exposures to Perfluoroalkyl Acids and Associations with Markers of Adiposity and Plasma Lipids in Infancy: An Odense Child Cohort Study	2020	Environ Health Perspect. 2020 Jul;128(7):77001. doi: 10.1289/EHP5184. Epub 2020 Jul 6.	Background: Perfluoroalkyl acids (PFAA) are repellants that cross the placental barrier, enabling interference with fetal programming. Maternal PFAA concentrations have been associated with offspring obesity and dyslipidemia in childhood and adulthood, but this association has not been studied in infancy. Objectives: We investigated associations between maternal PFAA concentrations and repeated markers of adiposity and lipid metabolism in infancy. Methods: In the prospective Odense Child Cohort, maternal pregnancy serum concentrations of five PFAA: Perfluorohexane sulfonic acid (PFHxS), perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), and perfluorodecanoic acid (PFDA) were measured in 649 women. Offspring were examined at birth (n=613) and at 3 months (n=602) and 18 months (n=503) of age. Total cholesterol, LDL, HDL, and triglyceride were evaluated at 3 months (n=262) and 18 months (n=198) of age. Mixed effects linear regression models estimated associations between PFAA and standardized (SDS) body mass index (BMI), ponderal index, and waist circumference. Associations between PFAA and body fat% (BF%) and plasma lipids SDS at 3 months and 18 months of age were investigated with linear regression models. Results: PFNA and PFDA were associated with higher BMI SDS [adjusted β=0.26; 95% confidence interval (CI): 0.03, 0.49 and β=0.58; 95% CI: –0.03, 1.19, respectively, for 1-ng/mL increases] and ponderal index SDS (β=0.36; 95% CI: 0.13, 0.59 and β=1.02; 95% CI: 0.40, 1.64, respectively) at 3 and 18 months of age (pooled) in girls. Corresponding estimates for boys were closer to the null but not significantly different from estimates for girls. In boys and girls (combined), PFNA and PFDA were associated with BF% at age 3 months (for 1-ng/mL PFDA, β=0.40; 95% CI: 0.04, 0.75), and PFDA was associated with total cholesterol SDS at 18 months (β=1.06; 95% CI: 0.08, 2.03) (n=83). Discussion: Prenatal PFAA were positively associated with longitudinal markers of adiposity and higher total cholesterol in infancy. These findings deserve attention in light of rising rates of childhood overweight conditions and dyslipidemia.	●	●								-		B	-
529	ヒト（内分泌系）	Jensen, R. C.; Glintborg, D.; Gade Timmermann, C. A.; Nielsen, F.; Kyhl, H. B.; Frederiksen, H.; Andersson, A. M.; Juul, A.; Sidelmann, J. J.; Andersen, H. R.; Grandjean, P.; Andersen, M. S.; Jensen, T. K.	Prenatal exposure to perfluorodecanoic acid is associated with lower circulating concentration of adrenal steroid metabolites during mini puberty in human female infants	2020	Environ Res. 2020 Mar;182:109101. doi: 10.1016/j.envres.2019.109101. Epub 2019 Dec 31.	BACKGROUND: Fetal programming of the endocrine system may be affected by exposure to perfluoroalkyl substances (PFAAs), as they easily cross the placental barrier. In vitro studies suggest that PFAAs may disrupt steroidogenesis. "Mini puberty" refers to a transient surge in circulating androgens, androgen precursors, and gonadotropins in infant girls and boys within the first postnatal months. We hypothesize that prenatal PFAA exposure may decrease the concentrations of androgens in mini puberty.OBJECTIVES: To investigate associations between maternal serum PFAA concentrations in early pregnancy and serum concentrations of androgens, their precursors, and gonadotropins during mini puberty in infancy.METHODS: In the prospective Odense Child Cohort, maternal pregnancy serum concentrations of five PFAAs: Perfluorohexane sulfonic acid (PFHxS), perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), and perfluorodecanoic acid (PFDA) were measured at median gestational week 12 (IQR: 10, 15) in 1628 women. Among these, offspring serum concentrations of dehydroepiandrosterone (DHEA), dehydroepiandrosterone-sulfate (DHEAS), androstenedione, 17-hydroxyprogesterone (17-OHP), testosterone, luteinizing (LH) and follicle stimulating hormones (FSH) were measured in 373 children (44% girls; 0.56 boys) at a mean age of 3.9 (±0.9 SD) months. Multivariate linear regression models were performed to estimate associations.RESULTS: A two-fold increase in maternal PFDA concentration was associated with a reduction in DHEA concentration by -0.196 (95% CI: -32.9%, -3.8%) in girls. In girls, also, the androstenedione and DHEAS concentrations were decreased, albeit non-significantly (p < 0.11), with a two-fold increase in maternal PFDA concentration. In boys, no significant association was found between PFAAs and concentrations of androgens, their precursors, and gonadotropins during mini puberty.CONCLUSION: Prenatal PFDA exposure was associated with significantly lower serum DHEA concentrations and possibly also with lower androstenedione and DHEAS concentrations in female infants at mini puberty. The clinical significance of these findings remains to be elucidated.	●	●								-	1	A	-
530	ヒト（生殖毒性）	530_Jensen, T. K. et; Andersen, L. B.; Kyhl, H. B.; Nielsen, F.; Christesen, H. T.; Grandjean, P.	Association between Perfluorinated Compound Exposure and Miscarriage in Danish Pregnant Women	2015	PLoS One. 2015 Apr 7;10(4):e0123496. doi: 10.1371/journal.pone.0123496. eCollection 2015.	Perfluorinated alkylated substances (PFAS) have been extensively used in consumer products and humans are widely exposed to these persistent compounds. A recent study found no association between exposure to perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS) and miscarriage, but no studies have examined adverse effect of the more recently introduced PFASs. We therefore conducted a case-control study within a population-based, prospective cohort during 2010-2012. Newly pregnant women residing in the Municipality of Odense, Denmark were invited to enroll in the Odense Child Cohort at their first antenatal visit before pregnancy week 12 Among a total of 2874 participating women, 88 suffered a miscarriage and 59 had stored serum samples, of which 56 occurred before gestational week 12 They were compared to a random sample (N=336) of delivering women, who had also donated serum samples before week 12 Using a case-control design, 51 of the women suffering a miscarriage were matched on parity and gestational day of serum sampling with 204 delivering women. In a multiple logistic regression with adjustment for age, BMI, parity and gestational age at serum sampling, women with the highest tertile of exposure to perfluorononanoic acid (PFNA) and perfluorodecanoic acid (PFDA) in pregnancy had odds ratios for miscarriage of 16.5 (95% CI 7.4-36.6-36.5) and 2.67 (1.31-5.44), respectively, as compared to the lowest tertile. In the matched data set, the OR were 37.9 (9.9-145.2) and 3.71 (1.60-8.60), respectively. The association with perfluorohexane sulfonic acid (PFHxS) was in the same direction, but not statistically significant, while no association was found with PFOA and PFOS. Our findings require confirmation due to the possible public health importance, given that all pregnant women are exposed to these widely used compounds.	●	●	●	●						-		B	-
531	ヒト（発生毒性）	531; Zhang, Y.; Zhu, L.; Deng, J.	Serum levels of perfluoroalkyl acids (PFAAs) with isomer analysis and their associations with medical parameters in Chinese pregnant women	2014	Environ Int. 2014 Mar;64:40-7. doi: 10.1016/j.envint.2013.12.001. Epub 2013 Dec 20.	Perfluoroalkyl acids (PFAAs) are a group of chemicals used for many applications and widely present in the environment and humans. In this study, serum levels of PFAAs and isomers of perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) were analyzed in 141 Chinese pregnant women. Among all the samples, total PFOS (ΣPFOS, mean concentration 7.32ng/mL) was predominant, followed by ΣPFOA (mean 4.78ng/mL) and perfluorodecanoate (PFDA, mean 1.45ng/mL). On average, the proportion of linear PFOS (n-PFOS) was 0.667 of ΣPFOS, which was higher than the general population, implying that maternal women could excrete branched PFOS isomers to the fetus by transplacental transfer. Moreover, the proportion of n-PFOS decreased significantly with the increasing concentration of ΣPFOS in the serum samples (r=-0.342, p<0.001). The mean proportion of n-PFOA in the serum samples was 99.0%, which was much higher than the technical ECF (electrochemical fluorination) products (ca. 70%). The small proportion of branched isomers of PFOA suggests that there is still a source of ECF PFOA in China. Significant correlations (p<0.005) were observed between the concentrations of some PFAAs with certain medical parameters in the pregnant women. For example, the levels of most perfluorinated carboxylic acids (PFCAs) were found to correlate with albumin significantly, which might be a sign of immunotoxicity of these chemicals. The adverse effects of PFAA exposure to pregnant women may increase the health risk of the fetus. Interestingly, not only the PFAA concentrations but also the percentages of PFOS and PFOA isomers were correlated with certain medical parameters. This implies that the compositions of PFOS or PFOA should be considered in human health risk assessment in the future.	●	●								-		C	-
532	ヒト（発生毒性）	Jin, Hangbiao; Mao, Lingling; Xie, Jiahui; Zhao, Meirong; Bai, Xiaoxia; Wen, Jie; Shen, Tao; Wu, Pengfei	Poly- and perfluoroalkyl substance concentrations in human breast milk and their associations with postnatal infant growth	2020	Sci Total Environ. 2020 Apr 15;713:136417. doi: 10.1016/j.scitotenv.2019.136417. Epub 2020 Jan 11.	Perfluoroalkyl carboxylates (PFCAs) and perfluoroalkyl sulfonates are widespread in human breast milk. However, the occurrence of chlorinated polyfluorinated ether sulfonates (Cl-PFESAs) and fluorotelomer alcohols (FTOHs) in breast milk and their effects on postnatal growth of infants through breast milk consumption are still not well known. This study characterized the occurrence of 16 poly- and perfluoroalkyl substances (PFASs) in breast milk from 174 women in Hangzhou, China and investigated the association between lactation exposure to these PFASs through breast milk consumption and the postnatal growth of infants. Our results showed that perfluorooctanoate (mean 87 pg/mL) was the predominant PFAS in breast milk, followed by perfluorohexanoate (41 pg/mL), 6:2 Cl-PFESA (28 pg/mL), and perfluorooctane sulfonate (25 pg/mL). The occurrence and levels of Cl-PFESAs in Chinese breast milk were firstly reported in the current study. The 8:2 and 10:2 FTOH were detected in half of breast milk samples, with the mean concentration of 9.0 pg/mL and 10 pg/mL, respectively. Breast milk concentrations of C(8)-C(10) PFCAs and 6:2 Cl-PFESA were negatively correlated with infant's length gain rate. Exposed to higher levels of 8:2 FTOH were correlated with decreased infant's weight gain rate. Daily intakes of PFASs via the consumption of breast milk were calculated for infants. Overall, this study firstly demonstrated that lactation exposure to C(8)-C(10) PFCAs, 8:2 FTOH, and 6:2 Cl-PFESA through breast milk consumption may affect the postnatal growth of infants.	●	●								-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
533	ヒト（発生毒性）	5; Mcconnell, R.; Catherine, C.; Xu, S.; Walker, D. I.; Stratakis, N.; Jones, D. P.; Miller, G. W.; Peng, C.; Conti, D. V.; Vos, M. B.; Chatzi, L.	Perfluoroalkyl substances and severity of nonalcoholic fatty liver in Children: An untargeted metabolomics approach	2020	Environ Int. 2020 Jan;134:105220. doi: 10.1016/j.envint.2019.105220. Epub 2019 Nov 16.	BACKGROUND: Toxicant-associated steatohepatitis has been described in adults but less is known regarding the role of toxicants in liver disease of children. Perfluoroalkyl substances (PFAS) cause hepatic steatosis in rodents, but few previous studies have examined PFAS effects on severity of liver injury in children.OBJECTIVES: We aimed to examine the relationship of PFAS to histologic severity of nonalcoholic fatty liver disease (NAFLD) in children.METHODS: Seventy-four children with physician-diagnosed NAFLD were recruited from Children's Healthcare of Atlanta between 2007 and 2015 Biopsy-based liver histological features were scored for steatosis, lobular and portal inflammation, ballooning, and fibrosis. Plasma concentrations of perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS) and perfluorohexane sulfonic acid (PFHxS), and untargeted plasma metabolomic profiling, were determined using liquid chromatography with high-resolution mass spectrometry. A metabolome-wide association study coupled with pathway enrichment analysis was performed to evaluate metabolic dysregulation associated with PFAS. A structural integrated analysis was applied to identify latent clusters of children with more severe form of NAFLD based on their PFAS levels and metabolite pattern.RESULTS: Patients were 7-19 years old, mostly boys (71%), Hispanic (51%), and obese (85%). The odds of having nonalcoholic steatohepatitis (NASH), compared to children with steatosis alone, was significantly increased with each interquartile range (IQR) increase of PFOS (OR: 3.32, 0.95 CI: 1.40-7.87) and PFHxS (OR: 4.18, 0.95 CI: 1.64-10.7). Each IQR increase of PFHxS was associated with increased odds for liver fibrosis (OR: 4.44, 0.95 CI: 1.34-14.8), lobular inflammation (OR: 2.87, 0.95 CI: 1.12-7.31), and higher NAFLD activity score (β coefficient 0.46; 0.95 CI: 0.03, 0.89). A novel integrative analysis identified a cluster of children with NASH, characterized by increased PFAS levels and altered metabolite patterns including higher plasma levels of phosphoethanolamine, tyrosine, phenylalanine, aspartate and creatine, and decreased plasma levels of betaine.CONCLUSIONS: Higher PFAS exposure was associated with more severe disease in children with NAFLD. PFAS may be an important toxicant contributing to NAFLD progression; however larger, longitudinal studies are warranted to confirm these findings.	●	●							-		B	-
534	ヒト（生殖毒性）	Joensen, U. N.; Bossi, R.; Leffers, H.; Jensen, A. A.; Skakkebæk, N. E.; Jørgensen, N.	Do perfluoroalkyl compounds impair human semen quality? Environ Health Perspect 117: 923-927	2009	Environ Health Perspect. 2009 Jun;117(6):923-7. doi: 10.1289/ehp.0800517. Epub 2009 Mar 2.	BACKGROUND: Perfluoroalkyl acids (PFAAs) are found globally in wildlife and humans and are suspected to act as endocrine disruptors. There are no previous reports of PFAA levels in adult men from Denmark or of a possible association between semen quality and PFAA exposure.OBJECTIVES: We investigated possible associations between PFAAs and testicular function. We hypothesized that higher PFAA levels would be associated with lower semen quality and lower testosterone levels.METHODS: We analyzed serum samples for levels of 10 different PFAAs and reproductive hormones and assessed semen quality in 105 Danish men from the general population (median age, 19 years).RESULTS: Considerable levels of perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), and perfluorohexane sulfonic acid were found in all young men (medians of 24.5, 4.9, and 6.6 ng/mL, respectively). Men with high combined levels of PFOS and PFOA had a median of 6.2 million normal spermatozoa in their ejaculate in contrast to 15.5 million among men with low PFOS-PFOA (p = 0.030). In addition, we found nonsignificant trends with regard to lower sperm concentration, lower total sperm counts, and altered pituitary-gonadal hormones among men with high PFOS-PFOA levels.CONCLUSION: High PFAA levels were associated with fewer normal sperm. Thus, high levels of PFAAs may contribute to the otherwise unexplained low semen quality often seen in young men. However, our findings need to be corroborated in larger studies.	●	●	●	●	●			●	-		B	-
535	ヒト（生殖毒性）	Joensen, U. N.; Veyrand, B.; Antignac, J. P.; Jensen, M. B.; Petersen, J. H.; Marchand, P.; Skakkebaek, N. E.; Andersson, A. M.; Le Bizec, B.; Jørgensen, N.	PFOS (perfluorooctanesulfonate) in serum is negatively associated with testosterone levels, but not with semen quality, in healthy men	2013	Hum Reprod. 2013 Mar;28(3):599-608. doi: 10.1093/humrep/des425. Epub 2012 Dec 18.	STUDY QUESTION Is exposure to perfluorinated compounds (PFCs) associated with testicular function (reproductive hormone levels and semen quality) in healthy men? SUMMARY ANSWER PFOS levels were significantly negatively associated with serum testosterone (total and calculated free), but not with any other reproductive hormones or semen quality. WHAT IS KNOWN ALREADY In animals, some PFCs have endocrine disrupting potential, but few studies have investigated PFCs in relation to human testicular function. Previously, we and others have observed a negative association between serum PFC levels and sperm morphology. The potential associations with reproductive hormones remain largely unresolved. STUDY DESIGN, SIZE, DURATION A cross-sectional study of 247 men was conducted during 2008–2009. PARTICIPANTS/MATERIALS, SETTING, METHODS Healthy men from the general population, median age of 19 years, gave serum and semen samples. Serum samples were analysed for total testosterone (T), estradiol (E), sex hormone-binding globulin (SHBG), luteinizing hormone (LH), follicle-stimulating hormone (FSH) and inhibin-B and 14 PFCs, including perfluorooctanesulfonate (PFOS). Semen samples were analysed according to the WHO criteria. MAIN RESULTS AND THE ROLE OF CHANCE PFOS levels were negatively associated with testosterone (T), calculated free testosterone (FT), free androgen index (FAI) and ratios of T/LH, FAI/LH and FT/LH. Other PFCs were found at lower levels than PFOS and did not exhibit the same associations. PFC levels were not significantly associated with semen quality. PFOS levels in these samples collected in 2008–2009 were lower than in our previous study of men participating in 2003. LIMITATIONS, REASONS FOR CAUTION Results were robust to adjustment for relevant confounders; however, the possibility of chance associations due to multiple testing or effects of uncontrolled confounding cannot be ruled out. WIDER IMPLICATIONS OF THE FINDINGS Our previous findings of decreased sperm morphology in the most highly PFC exposed men were not replicated, possibly due to a lack of highly exposed individuals; however, a recent independent study also did corroborate such an inverse association. The negative association between serum PFOS and testosterone indicates that testosterone production may be compromised in individuals with high PFOS exposure. STUDY FUNDING/COMPETING INTEREST(S) The authors received financial support from the European Commission (DEER, FP7-2007-212844), the Danish Agency for Science, Technology and Innovation (grant nos. 27107068 and 09-067180), Rigshospitalet (grant	●								-		B	-
536	ヒト（生殖毒性）	Jørgensen, K. T.; Specht, I. O.; Lenters, V.; Bach, C. C.; Rylander, L.; Jönsson, B. A.; Lindh, C. H.; Giwercman, A.; Heederik, D.; Toft, G.; Bonde, J. P.	Perfluoroalkyl substances and time to pregnancy in couples from Greenland, Poland and Ukraine	2014	Environ Health. 2014 Dec 22;13:116. doi: 10.1186/1476-069X-13-116.	BACKGROUND: Perfluoroalkyl substances (PFAS) are suggested to affect human fecundity through longer time to pregnancy (TTP). We studied the relationship between four abundant PFAS and TTP in pregnant women from Greenland, Poland and Ukraine representing varying PFAS exposures and pregnancy planning behaviors.METHODS: We measured serum levels of perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), perfluorohexane sulfonic acid (PFHxS) and perfluorononanoic acid (PFNA) in 938 women from Greenland (448 women), Poland (203 women) and Ukraine (287 women). PFAS exposure was assessed on a continuous logarithm transformed scale and in country-specific tertiles. We used Cox discrete-time models and logistic regression to estimate fecundability ratios (FRs) and infertility (TTP >13 months) odds ratios (ORs), respectively, and 0.95 confidence intervals (CI) according to PFAS levels. Adjusted analyses of the association between PFAS and TTP were done for each study population and in a pooled sample.RESULTS: Higher PFNA levels were associated with longer TTP in the pooled sample (log-scale FR = 0.80; 0.95 CI 0.69-0.94) and specifically in women from Greenland (log-scale FR = 0.72; 0.95 CI 0.58-0.89). ORs for infertility were also increased in the pooled sample (log-scale OR = 1.53; 0.95 CI 1.08-2.15) and in women from Greenland (log-scale OR = 1.97; 0.95 CI 1.22-3.19). However, in a sensitivity analysis of primiparous women these associations could not be replicated. Associations with PFNA were weaker for women from Poland and Ukraine. PFOS, PFOA and PFHxS were not consistently associated with TTP.CONCLUSIONS: Findings do not provide consistent evidence that environmental exposure to PFAS is impairing female fecundity by delaying time taken to conceive.	●	●	●	●			●		-		B	-
537	ヒト（発生毒性）	Karlsen, M.; Grandjean, P.; Weihe, P.; Steuerwald, U.; Oulhote, Y.; Valvi, D.	Early-life exposures to persistent organic pollutants in relation to overweight in preschool children	2017	Reprod Toxicol. 2017 Mar;68:145-153. doi: 10.1016/j.reprotox.2016.08.002. Epub 2016 Aug 3.	Current knowledge on obesogenic effects of persistent organic pollutants (POPs) is equivocal. We therefore evaluated the associations between early-life POP exposures and body mass index (BMI) in 444 Faroese children born in 2007-2009. POPs were measured in maternal 2-week postpartum serum and child age-5 serum. Linear regression and generalised linear models assessed the associations with continuous and dichotomous BMI z-scores, respectively, at ages 18 months and/or 5 years. Maternal serum concentrations of HCB, PFOS and PFOA were associated with increased BMI z-scores and/or overweight risk (i.e. BMI z-score≥85th WHO percentile). No clear association was found for maternal serum-PCBs, p,p'-DDE, PFHxS, PFNA and PFDA. In cross-sectional analyses, we observed a pattern of inverse associations between child serum-POPs and BMI z-scores at age 5, perhaps due to reverse causation that requires attention in future prospective analyses. Findings in this recent cohort support a role of maternal exposure to endocrine disruptors in the childhood obesity epidemic.	●	●	●	●					-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
538	ヒト（発生毒性）	Kashino, I.; Sasaki, S.; Okada, E.; Matsuura, H.; Goudarzi, H.; Miyashita, C.; Okada, E.; Ito, Y. M.; Araki, A.; Kishi, R.	Prenatal exposure to 11 perfluoroalkyl substances and fetal growth: A large-scale, prospective birth cohort study	2020	Environ Int. 2020 Mar;136:105355. doi: 10.1016/j.envint.2019.105355. Epub 2020 Feb 4.	BACKGROUND: Prenatal maternal exposure to perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) has been reportedly associated with decreased birth weight. Although a majority of epidemiological studies concerning perfluoroalkyl substances (PFAS) have focused on PFOS and PFOA, epidemiological studies of PFAS with longer carbon chains are scarce. In this study, we investigated whether prenatal maternal exposure to 11 PFAS, in particular those with longer carbon chains, is associated with fetal growth.METHODS: The study included 1985 mother-infant pairs (inclusive of preterm and post-term infants), who enrolled in a large-scale, prospective birth cohort study in any of the 37 hospitals in Hokkaido, Japan between 2003 and 2009 The concentration of 11 PFAS was measured in maternal plasma collected during the third trimester of pregnancy, using ultra-performance liquid chromatography in combination with triple quadrupole mass spectrometry. Associations between the measured PFAS values and weight, length, and head circumference of all newborns at birth were examined using multiple regression analyses with adjustment for potential confounders based on data collected from medical records, questionnaires, and those for maternal plasma samples.RESULTS: Of the 11 PFAS analyzed, prenatal perfluorononanoic acid (PFNA) [per log10-unit: regression coefficient (β) = -96.2 g, 0.95 confidence intervals (95% CI), -165.3 to -27.1]and perfluorodecanoic acid (PFDA) (β = -72.2 g, 0.95 CI, -138.1 to -6.3) concentrations were inversely associated with birth weight. Furthermore, PFNA concentrations were inversely associated with birth length (per Log10 unit: β = -0.48 cm, 0.95 CI; - 0.86 to -0.11). Maternal perfluorotridecanoic acid (PFTrDA) exposure showed a significant inverse association with birth weight only for female infants (per Log10 unit: β = -99.8 g, 0.95 CI, - 193.7 to -6.0) (P for interaction = 0.04).CONCLUSIONS: Our findings suggest that prenatal, maternal exposure to PFAS with longer carbon chains tends to be inversely associated with birth size of newborn infants, which may indicate that these commercially used compounds have an adverse effect on fetal growth.	●	●							-		B	-
539	ヒト（生殖毒性）	Kim, Y. R.; White, N.; Bräunig, J.; Vijayasarathy, S.; Mueller, J. F.; Knox, C. L.; Harden, F. A.; Pacella, R.; Toms, L. L.	The relationship between perfluoroalkyl substances concentrations and thyroid function in early childhood: A prospective cohort study	2020	Environ Res. 2020 Nov;190:109963. doi: 10.1016/j.envres.2020.109963. Epub 2020 Jul 21.	Background: Exposure to perfluoroalkyl substances (PFAS) has been suggested to affect thyroid function; however, data on early-life exposure and thyroid function in early childhood are scarce. We investigated the cross-sectional and longitudinal relationships of early-life exposure to PFAS with thyroid function at 2, 4, and 6 years of age. Methods: This study used data on PFAS exposure and thyroid function from the Environment and Development of Children (EDC) cohort study. A total of 660 children who visited at least once at 2, 4, or 6 years of age (381 children aged 2 years, 569 children aged 4 years, and 511 children aged 6 years) were included in this study. Serum thyrotropin (TSH) levels were measured at 2, 4, and 6 years of age. The relationship of serum PFAS (sPFAS) concentrations with TSH levels at the three time points was assessed by repeated-measure analysis using linear mixed models. The serum levels of free thyroxine (fT4) and triiodothyronine (T3) were measured once (at 6 years of age). The relationship of sPFAS with fT4 and T3 levels at 6 years of age was investigated by linear regression analyses. Results: None complained of hyper- or hypothyroid symptoms with normal fT4 and T3 levels. Repeated-measure analysis showed that TSH levels at 2, 4, and 6 years of age were inversely associated with serum perfluorononanoic acid (sPFNA), after adjusting for age, sex, and/or dietary iodine intake (p < 0.05). When stratified by sex, TSH levels were inversely associated with serum perfluorooctanoic acid (sPFOA) in boys and sPFNA in girls (p < 0.05 for both). fT4 levels at 6 years of age were positively related to sPFNA and serum perfluorohexane sulfonic acid at 2 years of age and sPFOA at 6 years of age, and T3 levels at 6 years of age showed positive relationships with serum perfluorodecanoic acid and serum perfluorooctane sulfonic acid at 6 years of age (p < 0.05 for all). When stratified by sex, similar positive relationships for sPFAS with fT4 and T3 levels were significant among boys only. Conclusions: A significant relationship was found between early-life exposure to PFAS and thyroid function. Early-life exposure to PFAS was associated with decreased TSH and increased fT4 or T3 levels among preschool-age children.	●	●							-		B	-
540	ヒト（発生毒性）	Kishi, Reiko; Kobayashi, Sachiko; Ikeno, Tamiko; Araki, Atsuko; Miyashita, Chihiro; Itoh, Sachiko; Sasaki, Seiko; Okada, Emiko; Kobayashi, Sumitaka; Kashino, Ikuko; Itoh, Kumiko; Nakajima, Sonomi	Ten years of progress in the Hokkaido birth cohort study on environment and children's health: cohort profile-updated 2013 [Review]	2013	Environ Health Prev Med. 2013 Nov;18(6):429-50. doi: 10.1007/s12199-013-0357-3.	The Hokkaido Study on Environment and Children's Health is an ongoing cohort study that began in 2002. The study consists of two prospective birth cohorts, the Sapporo cohort (n = 514) and the Hokkaido large-scale cohort (n = 20,940). The primary goals of this study are to first examine the potential negative effects of perinatal environmental chemical exposures on birth outcomes, including congenital malformations and growth retardation; second, to evaluate the development of allergies, infectious diseases and neurodevelopmental disorders and perform longitudinal observations of the children's physical development to clarify the causal relationship between these outcomes and environmental chemicals; third, to identify individuals genetically susceptible to environmental chemicals; finally, to identify the additive effects of various environmental factors in our daily life, such as secondhand smoke exposure or low folate intake during early pregnancy. In this paper, we introduce our recent progress in the Hokkaido study with a cohort profile updated in 2013. For the last ten years, we followed pregnant women and their offspring, measuring various environmental chemicals, i.e., PCB, OH-PCB and dioxins, PFCs (Perfluorinated Compounds), Organochlorine pesticides, Phthalates, bisphenol A and mercury. We discovered that the concentration of toxic equivalents (TEQ) of dioxin and other specific congeners of PCDF or PCDD have effects on birth weight, infants' neurodevelopment and immune function. There were significant gender differences in these effects; our results suggest that male infants have more susceptibility to those chemical exposures than female infants. Interestingly, we found maternal genetic polymorphisms in AHR, CYP1A1 or GSTs that significantly modified the dioxin concentrations in maternal blood, suggesting different dioxin accumulations in the bodies of individuals with these genotypes, which would lead to different dioxin exposure levels. These genetic susceptibility factors influenced the body size of children born from mothers that either smoked or were passively exposed to tobacco smoke. Further studies investigating the correlation between epigenetics, the effects of intrauterine exposure to environmental chemicals and developmental factors related to health and disease are warranted.	●	●							-		B	-
541	ヒト（発生毒性）	Kishi, R.; Nakajima, T.; Goudarzi, H.; Kobayashi, S.; Sasaki, S.; Okada, E.; Miyashita, C.; Itoh, S.; Araki, A.; Ikeno, T.; Iwasaki, Y.; Nakazawa, H.	The association of prenatal exposure to perfluorinated chemicals with maternal essential and long-chain polyunsaturated fatty acids during pregnancy and the birth weight of their offspring: the hokkaido study	2015	Environ Health Perspect. 2015 Oct;123(10):1038-45. doi: 10.1289/ehp.1408834. Epub 2015 Apr 3.	BACKGROUND: Fatty acids (FAs) are essential for fetal growth. Exposure to perfluorinated chemicals (PFCs) may disrupt FA homeostasis, but there is no epidemiological data regarding associations of PFCs and FA concentrations.OBJECTIVES: We estimated associations between perfluorooctane sulfonate (PFOS)/perfluorooctanoate (PFOA) concentrations and maternal levels of FAs and triglyceride (TG) and birth size of the offspring.METHODS: 306 mother-child pairs were analyzed in this birth cohort between 2002 and 2005 in Japan. The prenatal PFOS and PFOA levels were measured in maternal serum samples by liquid chromatography-tandem mass spectrometry. Maternal blood levels of 9 FAs and TG were measured by gas chromatography-mass spectrometry and TG-IE kits, respectively. Information of infants' birth size were obtained from participant medical records.RESULTS: The median PFOS and PFOA levels were 5.6 and 1.4 ng/mL, respectively. In the fully adjusted model, including maternal age, parity, annual household income, blood sampling period, alcohol consumption and smoking during pregnancy, PFOS, not PFOA, had a negative association with the levels of palmitic, palmitoleic, oleic, linoleic, α-linolenic, and arachidonic acids (p <0.005) and TG (p value=0.016). Females weighed 186.6 g less in mothers whose PFOS levels were in the fourth quartile compared to the first quartile (95% CI: -363.4, -9.8). We observed no significant association between maternal levels of PFOS and birth weight of male infants.CONCLUSIONS: Our data suggest an inverse association between PFOS exposure and polyunsaturated FA levels in pregnant women. We also found a negative association between maternal PFOS levels and female birth weight.	●	●		●			●		-		B	-
542	ヒト（発生毒性）	Kobayashi, S.; Azumi, K.; Goudarzi, H.; Araki, A.; Miyashita, C.; Kobayashi, S.; Itoh, S.; Sasaki, S.; Ishizuka, M.; Nakazawa, H.; Ikeno, T.; Kishi, R.	Effects of prenatal perfluoroalkyl acid exposure on cord blood IGF2/H19 methylation and ponderal index: The Hokkaido Study	2017	J Expo Sci Environ Epidemiol. 2017 May;27(3):251-259. doi: 10.1038/jes.2016.50. Epub 2016 Aug 24.	Prenatal exposure to perfluoroalkyl acids (PFAAs) influences fetal growth and long-term health. However, whether PFAAs affect offspring DNA methylation patterns to influence health outcomes is yet to be evaluated. Here, we assessed effect of prenatal PFAA exposure on cord blood insulin-like growth factor 2 (IGF2), H19, and long interspersed element 1 (LINE1) methylation and its associations with birth size. Mother-child pairs (N=177) from the Hokkaido Study on Environment and Children's Health were included in the study. Perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) levels in maternal serum were measured by liquid chromatography-tandem mass spectrometry. IGF2, H19, and LINE1 methylation in cord blood DNA was determined by pyrosequencing. After full adjustment in multiple linear regression models, IGF2 methylation showed a significant negative association with log-unit increase in PFOA (partial regression coefficient=-0.73; 0.95 confidence interval: -1.44 to -0.02). Mediation analysis suggested that reduced IGF2 methylation explained ~21% of the observed association between PFOA exposure and reduced ponderal index of the infant at birth. These results indicated that the effects of prenatal PFOA exposure could be mediated through DNA methylation. Further study will be required to determine the potential for long-term adverse health effects of reduced IGF2 methylation induced by PFOA exposure.	●	●		●					-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
543	ヒト（発生毒性）	Koshy, T. T.; Attina, T. M.; Ghassabian, A.; Gilbert, J.; Burdine, L. K.; Marmor, M.; Honda, M.; Chu, D. B.; Han, X.; Shao, Y.; Kannan, K.; Urbina, E. M.; Trasande, L.	Serum perfluoroalkyl substances and cardiometabolic consequences in adolescents exposed to the World Trade Center disaster and a matched comparison group	2017	Environ Int. 2017 Dec;109:128-135. doi: 10.1016/j.envint.2017.08.003. Epub 2017 Sep 8.	BACKGROUND: Large amounts of various chemical contaminants, including perfluoroalkyl substances (PFASs), were released at the time of the World Trade Center (WTC) disaster. Thousands of children who lived and/or attended school near the disaster site were exposed to these substances but few studies have examined the possible consequences related to these exposures.OBJECTIVES: To examine the relationship of PFASs serum levels with cardiometabolic profile in children and adolescents enrolled in the World Trade Center Health Registry (WTCHR) and a matched comparison group.METHODS: We evaluated WTCHR enrollees who resided in New York City and were born between September 11, 1993 and September 10, 2001, and a matched comparison group consisting of individuals who were ineligible for WTCHR participation upon distance of their home, school or work from the WTC and lack of participation in rescue and recovery activities. Matching was based on date of birth, sex, race, ethnicity, and income. We assessed exposure to PFASs, as measured by serum levels and association with cardiometabolic profile as measured by arterial wall stiffness, body mass index, insulin resistance, fasting total cholesterol, HDL, LDL and triglycerides.RESULTS: A total of 402 participants completed the study and serum samples were analyzed from 308 participants, 123 in the WTCHR group and 185 in the comparison group. In multivariable regression analysis, after adjusting for relevant confounders, we observed a significant, positive association of perfluorooctanoic acid (PFOA) with triglycerides (beta coefficient=0.14, 0.95 CI: 0.02, 0.27, 0.151 change), total cholesterol (beta coefficient=0.09, 0.95 CI: 0.04, 0.14, 0.092 change), and LDL cholesterol (beta coefficient=0.11, 0.95 CI: 0.03, 0.19, 0.115 change). Perfluorohexanesulfonic acid levels were associated with decreased insulin resistance (beta coefficient=-0.09, 0.95 CI: -0.18, -0.003, -0.086 change); PFOA and perfluorononanoic acid were associated with increased brachial artery distensibility.CONCLUSIONS: This research adds to our knowledge of the physical health impacts in a large group of children exposed to the WTC disaster. Abnormal lipid levels in young adults might be an early marker of atherosclerosis and cardiovascular diseases and our findings highlight the importance of conducting longitudinal studies in this population.	●	●		●						-		B	-
544	ヒト（発生毒性）	Kristensen S.L. ; Ramlau-Hansen, C H; Ernst, E; Olsen, S F; Bonde, J P; Vested, A; Halldorsson, T I; Becher, G; Haug, L S; Toft, G	Long-term effects of prenatal exposure to perfluoroalkyl substances on female reproduction	2013	Hum Reprod. 2013 Dec;28(12):3337-48. doi: 10.1093/humrep/det382. Epub 2013 Oct 15.	STUDY QUESTION: Does prenatal exposure to perfluoroalkyl substances (PFASs) have long-term effects on female reproductive function?. SUMMARY ANSWER: Our results suggest an association between in utero exposure to perfluorooctanoic acid (PFOA) and delay in age of menarche. WHAT IS KNOWN ALREADY: Previous cross-sectional studies have reported possible effects of PFASs on female reproduction including reduced fecundity, delayed puberty and accelerated age at menopause. Only limited data exist from follow-up studies on long-term implications of prenatal exposure to PFASs. STUDY DESIGN, SIZE, DURATION: In this study we used data from a Danish population-based cohort established in 1988-1989. Of 1212 eligible pregnant women, 965 participated. Follow-up was initiated in 2008 on the female offspring at ~20 years of age. Three hundred and sixty seven (84%) daughters answered a questionnaire and 267 (61%) daughters furthermore attended clinical examinations which were conducted in 2008-2009. PARTICIPANTS/MATERIALS, SETTING, METHODS: The final study population consisted of 343 daughters of which 254 had attended the clinical examinations and 89 had answered the questionnaire only. Levels of PFASs in maternal serum from pregnancy week 30 were used as a measure of prenatal exposure and related to age of menarche, menstrual cycle length, levels of reproductive hormones and follicle number of the daughters. Data were divided into three groups according to tertiles of maternal concentrations of PFASs (low, medium, high). MAIN RESULTS AND THE ROLE OF CHANCE: In adjusted regression analyses, daughters exposed to higher levels of PFOA in utero had a 5.3 (95% confidence interval: 1.3; 9.3) months later age of menarche compared with the reference group of lower PFOA. Crude (P = 0.05) and adjusted (P = 0.01) trend tests also indicated a relationship between higher prenatal PFOA exposure and delay of menarche. LIMITATIONS, REASONS FOR CAUTION: We did not measure the exact amount of PFASs to which the daughters had been exposed prenatally. Instead we used PFAS concentrations in maternal serum as surrogates. However, PFASs are efficiently transferred to the fetus via placenta. Information on age of menarche was collected retrospectively but the time interval for recall in our study was relatively short (2-10 years). The remaining outcome measures depended on participation in clinical examination which reduced the number of observations leading to limited statistical power and risk of selection bias. WIDER IMPLICATIONS OF THE FINDINGS: Since PFASs can be detected in humans all over the world, effects of prenatal exposure on female reproductive function later in life may have wide health implications. STUDY FUNDING/COMPETING INTEREST(S): The study was supported by the Danish Council for Independent Research (271-05-0296, 09-065631), the Danish Ministry of Interior and Health (0-302-02-18/5), the Danish Council for Strategic Research (09-067124 (Centre for Fetal Programming), 09-063072, 2101-06-0005), the Novo Nordisk Foundation, the Aarhus University Research Foundation, the Frimodt-Heineke Foundation, the Foundation of Maria Dorthea and Holger From, the Beckett-Foundation, the Research Grant of Organon and the Foundation of Lily Benthine Lund. There are no competing interests. TRIAL REGISTRATION NUMBER: Not applicable.	●	●		●						-		B	-
545	ヒト（生殖毒性）	Kvist, L.; Giwercman, Y. L.; Jönsson, B. A.; Lindh, C. H.; Bonde, J. P.; Toft, G.; Strucinski, P.; Pedersen, H. S.; Zvyezday, V.; Giwercman, A.	Serum levels of perfluorinated compounds and sperm Y:X chromosome ratio in two European populations and in Inuit from Greenland	2012	Reprod Toxicol. 2012 Dec;34(4):644-50. doi: 10.1016/j.reprotox.2012.09.007. Epub 2012 Oct 5.	This study investigated whether perfluorooctanoic acid (PFOA) and perfluorooctanesulfonate (PFOS), which exhibit reproductive toxicity in experimental animals, affect sperm sex chromosome ratio. The Y:X ratio was determined by fluorescence in situ hybridization. Serum concentrations of PFOA and PFOS were measured in 607 men from Greenland, Poland and Ukraine using liquid chromatography-tandem mass spectrometry. Data was analyzed by linear and nonlinear regression. We observed no associations between PFOA and Y:X ratio (p=0.845 in a linear model, p=0.296 in a nonlinear model). A positive nonlinear association between PFOS and Y:X ratio was observed (p=0.016), with no association in a linear model (p=0.118). Analyzing the populations separately, a negative trend between categorized PFOS exposure and Y:X ratio was observed for the Inuit (B=-0.002, p=0.044). In conclusion, there was a negative trend between Y:X ratio and PFOS in the Inuit, while there was no association between PFOA and the Y:X ratio in adult men.	●	●		●						-		B	-
546	ヒト（生殖毒性）	Kwon, E. J.; Shin, J. S.; Kim, B. M.; Shah-Kulkarni, S.; Park, H.; Kho, Y. L.; Park, E. A.; Kim, Y. J.; Ha, E. H.	Prenatal exposure to perfluorinated compounds affects birth weight through GSTM1 polymorphism	2016	J Occup Environ Med. 2016 Jun;58(6):e198-205. doi: 10.1097/JOM.0000000000000739.	OBJECTIVE: The aim of this study was to investigate the effect of genetic polymorphisms on the association of prenatal exposure to perfluorinated compounds (PFCs) with birth weight.METHODS: We analyzed the level of eight PFCs in cord blood and two genetic polymorphisms in maternal blood of 268 subjects.RESULTS: Concentrations of perfluorooctanoic acid, perfluorooctane sulfonate, perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), and perfluoroundecanoic acid (PFUnDA) showed significant association with a decrease in birth weight ($P < 0.05$). In mothers with glutathione S-transferase M1 (GSTM1) null genotype, concentrations of PFNA, PFDA, and PFUnDA showed significantly negative association with birth weight ($P < 0.05$).CONCLUSION: Our findings indicated that GSTM1 polymorphism might affect the association between exposure to PFCs and birth weight, suggesting the effect of genetic susceptibility on the relationship between prenatal PFCs exposure and birth outcomes.	●	●	●							-		B	-
547	ヒト（発生毒性）	Lai, Keng Po; Li, Jing Woei; Cheung, Angela; Li, Rong; Billah, Md Baki; Chan, Ting Fung; Wong, Chris Kong Chu	Transcriptome sequencing reveals prenatal PFOS exposure on liver disorders	2017	Environ Pollut. 2017 Apr;223:416-425. doi: 10.1016/j.envpol.2017.01.041. Epub 2017 Jan 25.	Perfluorooctane sulfonate (PFOS), a hepatic toxicant and a potential hepatocarcinogen, is commonly used in industrial products. The widespread contamination of PFOS in human maternal and cord blood has raised concerns about its potential risks to the fetus. It is believed that adverse environmental exposure during the critical period of embryo development can have long-lasting consequences in later life. In this report, we used transcriptome sequencing, followed by bioinformatics analysis, to elucidate the potential hepatotoxic and hepatocarcinogenic effects of prenatal PFOS exposure in the fetus. Our results demonstrated that prenatal PFOS exposure could activate the synthesis and metabolism of fatty acids and lipids, leading to liver damage and interference with liver development in the fetus. In addition, a number of cancer-promoting signaling pathways, including Wnt/β-catenin, Rac, and TGF-β, were found to be activated in the fetal liver. More importantly, hepatic transaminase activity, including aspartate aminotransferase and alanine transaminase activity, was induced in the liver of mice offspring after prenatal PFOS exposure. For the first time, our results demonstrate that the hepatotoxic effects of prenatal exposure to PFOS may predispose to a long-term liver disorder in the offspring.	●	●								-		B	-
548	ヒト（発生毒性）	Lauritzen, H. B.; Larose, T. L.; Øien, T.; Sandanger, T. M.; Odland, J. Ø.; van de Bor, M.; Jacobsen, G. W.	Maternal serum levels of perfluoroalkyl substances and organochlorines and indices of fetal growth: a Scandinavian case-cohort study	2017	Pediatr Res. 2017 Jan;81(1-1):33-42. doi: 10.1038/pr.2016.187. Epub 2016 Sep 22.	BACKGROUND: The associations between prenatal exposure to endocrine disruptive chemicals (EDCs) and fetal growth are inconsistent, and few studies have considered small-for-gestational-age (SGA) birth as an outcome. Our current study of Scandinavian parous women aimed to address these inconsistencies and gaps in the literature.METHODS: This case-cohort study included 424 mother-child pairs who participated in a prospective, multi-center study of parous women in Norway (Trondheim and Bergen) and Sweden (Uppsala). We used linear and logistic regression with 0.95 confidence intervals (CIs) to analyze the associations between two perfluoroalkyl substances (PFASs) and five organochlorines (OCs) from early second trimester and indices of fetal growth.RESULTS: Among Swedish women, prenatal exposure to perfluorooctanoate (PFOA), polychlorinated biphenyl (PCB) 153 and hexachlorobenzene (HCB) were associated with higher odds for SGA birth. We found stronger associations among Swedish male offspring. In the Norwegian cohort, we found no significant associations between EDC exposure and indices of fetal growth.CONCLUSIONS: Some populations may be more vulnerable to EDCs, possibly due to differences in exposure levels, exposure sources and/or modifiable lifestyle factors. Male offspring may be more vulnerable to endocrine disruption.	●	●		●			●			-		B	-
549	ヒト（発生毒性）	Lee, E. S.; Han, S.; Oh, J. E.	Association between perfluorinated compound concentrations in cord serum and birth weight using multiple regression models	2016	Reprod Toxicol. 2016 Jan;59:53-9. doi: 10.1016/j.reprotox.2015.10.020. Epub 2015 Nov 10.	The effects of exposure to the perfluoroalkyl and polyfluoroalkyl substances (PFASs) perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) on birth weight have been examined in several studies, but other PFASs have not been considered. We conducted a cross-sectional survey of newborns in Seoul, South Korea, collecting 118 serum samples, for 85 of which we had a full range of information. We conducted multiple regression analyses to examine the association between nine PFAS concentrations in cord serum and birth weight. Seven PFASs were found in cord serum, PFOA and PFOS being dominant, with mean concentrations of 1.11 and 0.87ng/mL, respectively. The adjusted birth weight changes (natural log) were -0.14 (95% confidence interval -0.33-0.03) for PFOS and -0.03 (95% confidence interval -0.25-0.18) for PFOA. None of the PFASs were statistically associated with birth weight in this population.	●	●		●						-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①抽出	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
550	ヒト（発生毒性）	Lee, Y. A.; Kim, J. H.; Jung, H. W.; Lim, Y. H.; Bae, S.; Kho, Y.; Hong, Y. C.; Shin, C. H.; Yang, S. W.	The serum concentrations of perfluoroalkyl compounds were inversely associated with growth parameters in 2-year old children	2018	Sci Total Environ. 2018 Jul 1;628-629:226-232. doi: 10.1016/j.scitotenv.2018.02.050. Epub 2018 Feb 13.	The relationship between the serum concentrations of perfluoroalkyl compounds (PFCs) and growth parameters was investigated in 2-year-old Korean children. The study included 361 children aged 2years (192 boys and 169 girls; 22-27months), born at term appropriate-for-gestational-age, who visited between 2012 and 2013 Growth parameters of height and weight, and serum samples were collected from 2-year-old children. Four PFCs (perfluorohexane sulfonic acid [PFHxS], perfluorooctane sulfonic acid [PFOS], perfluorooctanoic acid [PFOA], and perfluorononanoic acid [PFNA]), perfluorodecanoic acid (PFDA), perfluorundecanoic acid (PFUnDA), and perfluoroheptanoic acid (PFHpA) were detected in >99, 93.4, 89.8, and 0.742 of the serum samples, respectively. The duration of breastfeeding was positively associated with the serum concentrations of ln-transformed PFHxS, PFOS, PFHpA, PFOA, PFNA, PFDA, and PFUnDA (all P<0.001). Height at 2years of age was inversely related to PFHxS, PFOS, PFOA, PFNA, and PFDA concentrations (adjusted β per ln unit [95% confidence interval, CI]: -0.84 [-1.26, -0.42], -0.77 [-1.27, -0.15], -0.91 [-1.36, -0.47], -0.48 [-1.40, -0.51], and -0.44 [-0.77, -0.10] cm, respectively), after adjusting for age, sex, and midparental height. Weight at 2years of age was inversely associated with PFNA (adjusted β per ln unit [95% CI]: -0.32 [-0.48, -0.15] kg), after adjusting for age, sex, and parental BMI. In conclusion, the serum concentrations of PFCs were inversely associated with growth parameters in 2-year-old children.	●	●							-		B	-
551	ヒト（生殖毒性）	Lenters, V.; Portengen, L.; Rignell-Hydbom, A.; Jönsson, B. A.; Lindh, C. H.; Piersma, A. H.; Toft, G.; Bonde, J. P.; Heederik, D.; Rylander, L.; Vermeulen, R.	Prenatal phthalate, perfluoroalkyl acid, and organochlorine exposures and term birth weight in three birth cohorts: Multi-pollutant models based on elastic net regression	2016	Environ Health Perspect. 2016 Mar;124(3):365-72. doi: 10.1289/ehp.1408933. Epub 2015 Jun 26.	Background: Some legacy and emerging environmental contaminants are suspected risk factors for intrauterine growth restriction. However, the evidence is equivocal, in part due to difficulties in disentangling the effects of mixtures. Objectives: We assessed associations between multiple correlated biomarkers of environmental exposure and birth weight. Methods: We evaluated a cohort of 1,250 term (≥ 37 weeks gestation) singleton infants, born to 513 mothers from Greenland, 180 from Poland, and 557 from Ukraine, who were recruited during antenatal care visits in 2002-2004. Secondary metabolites of diethylhexyl and diisononyl phthalates (DEHP, DiNP), eight perfluoroalkyl acids, and organochlorines (PCB-153 and p,p´-DDE) were quantifiable in 72-100% of maternal serum samples. We assessed associations between exposures and term birth weight, adjusting for co-exposures and covariates, including prepregnancy body mass index. To identify independent associations, we applied the elastic net penalty to linear regression models. Results: Two phthalate metabolites (MEHHP, MOiNP), perfluorooctanoic acid (PFOA), and p,p´-DDE were most consistently predictive of term birth weight based on elastic net penalty regression. In an adjusted, unpenalized regression model of the four exposures, 2-SD increases in natural log-transformed MEHHP, PFOA, and p,p´-DDE were associated with lower birth weight: -87 g (95% CI: -137, -340 per 1.70 ng/mL), -43 g (95% CI: -108, 23 per 1.18 ng/mL), and -135 g (95% CI: -192, -78 per 1.82 ng/g lipid), respectively; and MOiNP was associated with higher birth weight (46 g; 95% CI: -5, 97 per 2.22 ng/mL). Conclusions: This study suggests that several of the environmental contaminants, belonging to three chemical classes, may be independently associated with impaired fetal growth. These results warrant follow-up in other cohorts.	●	●	●	●					-		B	-
552	ヒト（生殖毒性）	Leter, G.; Consales, C.; Eleuteri, P.; Uccelli, R.; Specht, I. O.; Toft, G.; Moccia, T.; Budillon, A.; Jönsson, B. A.; Lindh, C. H.; Giwercman, A.; Pedersen, H. S.; Ludwicki, J. K.; Zviezdai, V.; Heederik, D.; Bonde, J. P.; Spanò, M.	Exposure to perfluoroalkyl substances and sperm DNA global methylation in Arctic and European populations	2014	Environ Mol Mutagen. 2014 Aug;55(7):591-600. doi: 10.1002/em.21874. Epub 2014 Jun 3.	Perfluoroalkyl substances (PFASs) are widely used in a variety of industrial processes and products, and have been detected globally in humans and wildlife. PFASs are suspected to interfere with endocrine signaling and to adversely affect human reproductive health. The aim of the present study was to investigate the associations between exposure to PFASs and sperm global methylation levels in a population of non-occupationally exposed fertile men. Measurements of PFASs in serum from 262 partners of pregnant women from Greenland, Poland and Ukraine, were also carried out by liquid chromatography tandem mass spectrometry. Perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), perfluorohexane sulfonic acid (PFHxS), and perfluorononanoic acid (PFNA) were detected in 0.97 of the blood samples. Two surrogate markers were used to assess DNA global methylation levels in semen samples from the same men: (a) average DNA methylation level in repetitive DNA sequences (Alu, LINE-1, Satα) quantified by PCR-pyrosequencing after bisulfite conversion; (b) flow cytometric immunodetection of 5-methyl-cytosines. After multivariate linear regression analysis, no major consistent associations between PFASs exposure and sperm DNA global methylation endpoints could be detected. However, since weak but statistically significant associations of different PFASs with DNA hypo- and hyper-methylation were found in some of the studied populations, effects of PFASs on sperm epigenetic processes cannot be completely excluded, and this issue warrants further investigation.	●	●							-		B	-
553	ヒト（内分泌系）	Lewis, R. C.; Johns, L. E.; Meeker, J. D.	Serum Biomarkers of Exposure to Perfluoroalkyl Substances in Relation to Serum Testosterone and Measures of Thyroid Function among Adults and Adolescents from NHANES 2011-2012	2015	Int J Environ Res Public Health. 2015 May 29;12(6):6098-114. doi: 10.3390/ijerph120606098.	Perfluoroalkyl substances (PFASs) are a group of environmentally-persistent chemicals that have been widely used in many industrial applications. There is human and animal evidence that PFASs may alter levels of reproductive and thyroid-related hormones. However, human studies on the potential age-related effects of PFASs on these outcomes among males and females are limited. We explored the relationship between serum PFASs and serum total testosterone (T), thyroid stimulating hormone (TSH), and free and total triiodothyronine (FT3, TT3) and thyroxine (FT4, TT4) among males and females 12 to 80 years of age from the 2011-2012 cycle of the National Health and Nutrition Examination Survey. Associations were assessed using multiple linear regression models that were stratified on sex and age categories. Effect estimates from the majority of the adjusted models were not statistically significant. However, exposure to PFASs may be associated with increases in FT3, TT3, and FT4 among adult females, but during adolescence, PFASs may be related to increases in TSH among males and decreases in TSH among females. No significant relationships were observed between PFASs and T in any of the models. These findings suggest that exposure to PFASs may disrupt thyroid hormone homeostasis.	●	●	●	●					●	-		1	A	-
554	ヒト（発生毒性）	Li, M.; Zeng, X. W.; Qian, Z. M.; Vaughn, M. G.; Sauvé, S.; Paul, G.; Lin, S.; Lu, L.; Hu, L. W.; Yang, B. Y.; Zhou, Y.; Qin, X. D.; Xu, S. L.; Bao, W. W.; Zhang, Y. Z.; Yuan, P.; Wang, J.; Zhang, C.; Tian, Y. P.; Nian, M.; Xiao, X.; Fu, C.; Dong, G. H.	Isomers of perfluorooctanesulfonate (PFOS) in cord serum and birth outcomes in China: Guangzhou Birth Cohort Study	2017	Environ Int. 2017 May;102:1-8. doi: 10.1016/j.envint.2017.03.006. Epub 2017 Mar 12.	Prior investigations on the associations of polyfluoroalkyl substances (PFASs) with fetal growth are mixed. Moreover, little research has accrued pertaining to the association between isomers of PFASs with gestational age and birth weight. To address this gap and present novel information, we conducted a study including 321 pairs of mothers and their infants recruited from Guangzhou, China. High performance liquid chromatography-mass spectrometry was utilized to analyze isomers of perfluorooctanesulfonate (PFOS), perfluorooctanoate (PFOA) along with other PFAS levels in cord serum samples. Mothers' and infants' characteristics were gathered from medical records. The resulting data revealed that higher PFOS, PFOA and isomers of PFOS were associated with lower birth weight. Per ln-unit (ng/mL) increase in cord serum total branched PFOS isomers was associated with a 126.3g (95% CI: -195.9, -56.8) reduction in the weight of infants at birth, while an ln-unit (ng/mL) increase of serum linear PFOS isomers (n-PFOS) was associated with a 57.2g (95% CI: -103.1, -11.3) reduction in the weight of infants at birth upon the subsequent adjustment for potential confounding variables. Notably, the association between cord PFAS level and birth weight was more pronounced in male infants. Furthermore, a positive association among branched PFOS isomers (1m-PFOS and 3+4+5m-PFOS) and gestational age was found. No associations could be found among other PFASs in conjunction with gestational age or birth weight. In conclusion, this investigation suggests that higher PFAS concentrations are associated with lower birth weight, and branched PFOS isomers show greater impact on infant birth weight than linear PFOS.	●	●		●					-		B	-
555	ヒト（発生毒性）	Lien, G. W.; Huang, C. C.; Shiu, J. S.; Chen, M. H.; Hsieh, W. S.; Guo, Y. L.; Chen, P. C.	Perfluoroalkyl substances in cord blood and attention deficit/hyperactivity disorder symptoms in seven-year-old children	2016	Chemosphere. 2016 Aug;156:118-127. doi: 10.1016/j.chemosphere.2016.04.102. Epub 2016 May 9.	OBJECTIVE: The effect of perfluoroalkyl substances (PFASs) on the development of neurotoxicity in children is still controversial. This study aimed to evaluate the association between in utero exposure to four PFASs and the development of neurobehavioral symptoms related to attention deficit hyperactivity disorder (ADHD) in early childhood.METHODS: Eligible study subjects were selected from the Taiwan Birth Panel Study and the Taiwan Early-Life Cohort, which enrolled a total of 1526 mother-infant pairs during 2004 and 2005 We collected umbilical cord blood and analyzed perfluorooctanoic acid (PFOA), perfluorooctanyl sulfonate (PFOS), perfluorononanoic acid (PFNA), and perfluoroundecanoic acid (PFUA) levels. When a child was 7 years old, to evaluate ADHD related neurobehavioral symptoms, their parents completed the Swanson, Nolan, and Pelham IV scale (SNAP-IV), the Child Behavior Checklist (CBCL), and the Strengths and Difficulties Questionnaire (SDQ) questionnaires. We used linear regression models with inverse probability weighting to explore the association between prenatal exposure to four PFASs and ADHD rating scores.RESULTS: A total of 282 subjects have completed the PFASs analysis and questionnaire survey. After adjusted for potential confounders, we observed that PFNA is inversely associated with inattention and oppositional defiant disorder of SNAP-IV, and hyperactivity/inattention of SDQ. No association between PFOA, PFOS, or PFUA and ADHD symptoms was found.CONCLUSIONS: Prenatal exposure to PFNA was found to associate with neurobehavioral symptoms related to ADHD among Asian seven-year-old children. Further studies are needed to elucidate the causal relationship.	●	●	●	●					-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ランク①	文献ランク②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
556	ヒト（生殖毒性）	Liew, Z.; Luo, J.; Nohr, E. A.; Bech, B. H.; Bossi, R.; Arah, O. A.; Olsen, J.	Maternal Plasma Perfluoroalkyl Substances and Miscarriage: A Nested Case-Control Study in the Danish National Birth Cohort	2020	Environ Health Perspect. 2020 Apr;128(4):47007. doi: 10.1289/EHP6202. Epub 2020 Apr 22.	BACKGROUNDPer- and polyfluoroalkyl substances (PFAS) are widespread persistent organic pollutants and endocrine disruptors. High doses of perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) exposure can cause pregnancy loss and infant deaths in animals, but the associations between PFAS exposures and risk of miscarriage in humans are not well studied.METHODSUsing a case-control study nested within the Danish National Birth Cohort (DNBC, 1996-2002), we compared 220 pregnancies ending in miscarriage during weeks 44917 of gestation, with 218 pregnancies resulting in live births. Levels of seven types of PFAS [PFOS, PFOA, perfluorohexane sulfonate (PFHxS), perfluoroheptane sulfonate (PFHpS), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), and perfluorooctanesulfonic acid (PFOSA)] were measured in maternal plasma collected in early gestation (mean gestational week 8). We estimated the odds ratios (ORs) and 0.95 confidence intervals (CIs) for miscarriage and each PFAS as a continuous variable or in quartiles, controlling for maternal age, parity, socio-occupational status, smoking and alcohol intake, gestational week of blood sampling, and maternal history of miscarriage. Stratification by parity and PFAS mixture analyses using weighted quantile sum (WQS) regression were also conducted.RESULTSWe observed a monotonic increase in odds for miscarriage associated with increasing PFOA and PFHpS levels. The ORs comparing the highest PFOA or PFHpS quartile to the lowest were 2.2 (95% CI: 1.2, 3.9) and 1.8 (95% CI: 1.0, 3.2). The ORs were also elevated for the second or third quartile of PFHxS or PFOS, but no consistent exposure-outcome pattern emerged. An interquartile range (IQR) increment in the WQS index of seven PFAS was associated with 0.64 higher odds for miscarriage (95% CI: 1.15, 2.34). The associations were stronger in parous women, while findings were inconsistent among nulliparous women.CONCLUSIONMaternal exposures to higher levels of PFOA, PFHpS, and PFAS mixtures were associated with the risk of miscarriage and particularly among parous women. Larger replication studies among nulliparous women are needed to allay concerns about confounding by reproductive history.	●	●							●	-		B	-
557	ヒト（発生毒性）	Liew, Z.; Ritz, B.; Bonefeld-Jørgensen, E. C.; Henriksen, T. B.; Nohr, E. A.; Bech, B. H.; Fei, C.; Bossi, R.; von Ehrenstein, O. S.; Streja, E.; Uldall, P.; Olsen, J.	Prenatal exposure to perfluoroalkyl substances and the risk of congenital cerebral palsy in children	2014	Am J Epidemiol. 2014 Sep 15;180(6):574-81. doi: 10.1093/aje/kwu179. Epub 2014 Aug 19.	Perfluoroalkyl substances (PFASs) are persistent pollutants and endocrine disruptors that may affect fetal brain development. We investigated whether prenatal exposure to PFASs increases the risk of congenital cerebral palsy (CP). The source population for this study includes 83389 liveborn singletons and mothers enrolled in the Danish National Birth Cohort during 1996-2002. We identified 156 CP cases by linking the cohort to the Danish National Cerebral Palsy Register, and we randomly selected 550 controls using a case-cohort design. We measured 16 PFASs in maternal plasma collected in early or midpregnancy, and 6 PFASs were quantifiable in more than 0.9 of the samples. We found a higher risk of CP in boys with higher maternal PFAS levels; per 1-unit (natural-log ng/mL) increase, the risk ratios were 1.7 (95% confidence interval: 1.0, 2.8) for perfluorooctane sulfonate and 2.1 (95% confidence interval: 1.2, 3.6) for perfluorooctanoic acid. We also observed a dose-response pattern of CP risk in boys per quartile of maternal level of perfluorooctane sulfonate and perfluorooctanoic acid (P for trend < 0.01). PFASs were associated with both unilateral and bilateral spastic CP subphenotypes. No association between PFASs and CP was found in girls. Prenatal exposures to PFASs may increase the risk of CP in boys, but the finding is novel and replication is needed.	●	●	●	●						-		B	-
558	ヒト（発達神経毒性）	Liew, Z.; Ritz, B.; von Ehrenstein, O. S.; Bech, B. H.; Nohr, E. A.; Fei, C.; Bossi, R.; Henriksen, T. B.; Bonefeld-Jørgensen, E. C.; Olsen, J.	Attention deficit/hyperactivity disorder and childhood autism in association with prenatal exposure to perfluoroalkyl substances: A nested case-control study in the Danish National Birth Cohort	2015	Environ Health Perspect. 2015 Apr;123(4):367-73. doi: 10.1289/ehp.1408412. Epub 2014 Dec 19.	BACKGROUND: Perfluoroalkyl substances (PFASs) are persistent pollutants found to be endocrine disruptive and neurotoxic in animals. Positive correlations between PFASs and neurobehavioral problems in children were reported in cross-sectional data, but findings from prospective studies are limited.OBJECTIVES: We investigated whether prenatal exposure to PFASs is associated with attention deficit/hyperactivity disorder (ADHD) or childhood autism in children.METHODS: Among 83389 mother-child pairs enrolled in the Danish National Birth Cohort during 1996-2002, we identified 890 ADHD cases and 301 childhood autism cases from the Danish National Hospital Registry and the Danish Psychiatric Central Registry. From this cohort, we randomly selected 220 cases each of ADHD and autism, and we also randomly selected 550 controls frequency matched by child's sex. Sixteen PFASs were measured in maternal plasma collected in early or mid-pregnancy. We calculated risk ratios (RRs) using generalized linear models, taking into account sampling weights.RESULTS: Perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) were detected in all samples; four other PFASs were quantified in ≥ 0.9 of the samples. We did not find consistent evidence of associations between mother's PFAS plasma levels and ADHD [per natural log nanograms per milliliter increase: PFOS RR = 0.87 (95% CI: 0.74, 1.02); PFOA RR = 0.98 (95% CI: 0.82, 1.16)] or autism [per natural log nanograms per milliliter increase: PFOS RR = 0.92 (95% CI: 0.69, 1.22); PFOA RR = 0.98 (95% CI: 0.73, 1.31)]. We found positive as well as negative associations between higher PFAS quartiles and ADHD in models that simultaneously adjusted for all PFASs, but these estimates were imprecise.CONCLUSIONS: In this study we found no consistent evidence to suggest that prenatal PFAS exposure increases the risk of ADHD or childhood autism in children.	●	●	●	●						-	1	A	-
559	ヒト（生殖毒性）	Lind, D. V.; Priskorn, L.; Lassen, T. H.; Nielsen, F.; Kyhl, H. B.; Kristensen, D. M.; Christesen, H. T.; Jørgensen, J. S.; Grandjean, P.; Jensen, T. K.	Prenatal exposure to perfluoroalkyl substances and anogenital distance at 3 months of age in a Danish mother-child cohort	2017	Reprod Toxicol. 2017 Mar;68:200-206. doi: 10.1016/j.reprotox.2016.08.019. Epub 2016 Aug 31.	In the Odense child cohort, serum concentrations of perfluorooctanesulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorohexane sulfonic acid (PFHxS), perfluorononanoic acid (PFNA), and perfluorodecanoic acid (PFDA) were measured in 638 pregnant women. Birth weight, head and abdominal circumferences and gestational age were determined. Anogenital distance (AGD), the distance from the anus to the genital organs, and penile width were measured 3 months after expected date of birth in 511 children. PFOS, PFHxS, PFNA and PFDA were associated with a decreased AGD in girls (p-trend<0.05) after adjusting for age and weight-for-age standard deviation score. PFOS in the highest quartile was associated with a 2.8mm (95% confidence intervals -4.5; -1.1) reduction in AGD in girls. No such tendencies were seen in boys. However, a tendency toward increased birth weight in girls and reduced birth weight in boys suggests that sex-dimorphic effects may occur from endocrine disrupting effects of these substances.	●	●	●	●						-		B	-
560	ヒト（発生毒性）	Liu, G.; Dhana, K.; Furtado, J. D.; Rood, J.; Zong, G.; Liang, L.; Qi, L.; Bray, G. A.; Dejonge, L.; Coull, B.; Grandjean, P.; Sun, Q.	Perfluoroalkyl substances and changes in body weight and resting metabolic rate in response to weight-loss diets: A prospective study	2018	PLoS Med. 2018 Feb 13;15(2):e1002502. doi: 10.1371/journal.pmed.1002502. eCollection 2018 Feb.	BACKGROUND: The potential endocrine-disrupting effects of perfluoroalkyl substances (PFASs) have been demonstrated in animal studies, but whether PFASs may interfere with body weight regulation in humans is largely unknown. This study aimed to examine the associations of PFAS exposure with changes in body weight and resting metabolic rate (RMR) in a diet-induced weight-loss setting.METHODS AND FINDINGS: In the 2-year POUNDS Lost randomized clinical trial based in Boston, Massachusetts, and Baton Rouge, Louisiana, that examined the effects of energy-restricted diets on weight changes, baseline plasma concentrations of major PFASs were measured among 621 overweight and obese participants aged 30-70 years. Body weight was measured at baseline and 6, 12, 18, and 24 months. RMR and other metabolic parameters, including glucose, lipids, thyroid hormones, and leptin, were measured at baseline and 6 and 24 months. Participants lost an average of 6.4 kg of body weight during the first 6 months (weight-loss period) and subsequently regained an average of 2.7 kg of body weight during the period of 44736 months (weight regain period). After multivariate adjustment, baseline PFAS concentrations were not significantly associated with concurrent body weight or weight loss during the first 6 months. In contrast, higher baseline levels of PFASs were significantly associated with a greater weight regain, primarily in women. In women, comparing the highest to the lowest tertiles of PFAS concentrations, the multivariate-adjusted mean weight regain (SE) was 4 -0.8 versus 2.1 -0.9 kg for perfluorooctanesulfonic acid (PFOS) (Ptrend = 0.01); 4.3 -0.9 versus 2.2 -0.8 kg for perfluorooctanoic acid (PFOA) (Ptrend = 0.007); 4.7 -0.9 versus 2.5 -0.9 kg for perfluorononanoic acid (PFNA) (Ptrend = 0.006); 4.9 -0.9 versus 2.7 -0.8 kg for perfluorohexanesulfonic acid (PFHxS) (Ptrend = 0.009); and 4.2 -0.8 versus 2.5 -0.9 kg for perfluorodecanoic acid (PFDA) (Ptrend = 0.03). When further adjusted for changes in body weight or thyroid hormones during the first 6 months, results remained similar. Moreover, higher baseline plasma PFAS concentrations, especially for PFOS and PFNA, were significantly associated with greater decline in RMR during the weight-loss period and less increase in RMR during the weight regain period in both men and women. Limitations of the study include the possibility of unmeasured or residual confounding by socioeconomic and psychosocial factors, as well as possible relapse to the usual diet prior to randomization, which could have been rich in foods contaminated by PFASs through food packaging and also dense in	●	●		●						-		B	-
561	ヒト（生殖毒性）	Liu, H.; Pan, Y.; Jin, S.; Li, Y.; Zhao, L.; Sun, X.; Cui, Q.; Zhang, B.; Zheng, T.; Xia, W.; Zhou, A.; Campana, A. M.; Dai, J.; Xu, S.	Associations of per-/polyfluoroalkyl substances with glucocorticoids and progestogens in newborns	2020	Environ Int. 2020 Jul;140:105636. doi: 10.1016/j.envint.2020.105636. Epub 2020 May 28.	Background: Exposure to per-/polyfluoroalkyl substances (PFASs) can disrupt endocrine hormones in humans. Prior studies have focused on the harmful effects of the two traditional per-/polyfluoroalkyl substances (PFASs), perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA). Other PFASs, used as the replacements of PFOS and PFOA, are widely and increasingly detected in humans. Whether these replacements influence glucocorticoids and progestogens in newborns remains unknown. Objective: To investigate the associations between exposures of PFOS, PFOA and their replacements and glucocorticoids and progestogens in newborns. Methods: We measured the concentrations of 13 PFASs, 3 glucocorticoids (11-deoxycortisol, cortisol and cortisone) and 2 progestogens [progesterone, 17-hydroxyprogesterone (17OHP)] in the cord sera of 374 neonates in a birth cohort from Wuhan, China, between 2013 and 2014. We evaluated the associations of each PFAS with glucocorticoids and progestogens using multiple linear regression models, and multiple comparisons were additionally corrected via false discovery rates (FDR). Results: Out of the 13 PFASs, 9 were detected in over 95% of cord sera. The Chinese specific PFOS replacement - 6:2 chlorinated polyfluorinated ether sulfonate (6:2 Cl-PFESA, trade name F-53B) was positively associated with 13.13% change in cortisol in girls (95% CI = 4.47%, 22.52%, for each IQR increase in 6:2 Cl-PFESA). Seven PFASs had positive associations with the precursor of cortisol, namely 11-deoxycortisol (percent change ranged from 6.41% to 11.24%, for each IQR increase in PFASs). Perfluorobutane sulfonate (PFBS) in cord sera was positively associated with progesterone in the linear model, whereas PFOS and perfluorohexane sulfonate (PFHxS) levels were associated with progesterone in the quartile models. No PFASs were related to 17OHP or cortisone. Conclusions: In this study, PFOS, PFOA and/or their replacements were positively associated with progesterone, cortisol and 11-deoxycortisol in newborns. These results suggested that not only PFOS and PFOA, but also other PFASs have potential impacts on glucocorticoids and progestogens in newborns.	●	●								-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献ラン①抽出	文献ラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
562	ヒト（生殖毒性）	Lopez-Espinosa, M. J.; Fletcher, T.; Armstrong, B.,en; Genser, B.; Dhatariya, K.; Mondal, D.; Ducatman, A.; Leonardi, G.	Association of Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS) with Age of Puberty among Children Living near a Chemical Plant	2011	Environ Sci Technol. 2011 Oct 1;45(19):8160-6. doi: 10.1021/es1038694. Epub 2011 May 2.	Animal studies suggest that perfluorocarbons (PFCs) may alter sexual maturation. Relationships of human PFC exposure with puberty are not clear. We conducted a cross-sectional study to investigate whether perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) were associated with indicators of sexual maturation in a 2005-2006 survey of residents with PFOA water contamination from the Mid-Ohio Valley. Participants were 3076 boys and 2931 girls aged 44791 years. They were classified as having reached puberty based on either hormone levels (total >50 ng/dL and free >5 pg/mL testosterone in boys and estradiol >20 pg/mL in girls) or onset of menarche. We estimated the odds of having reached puberty classified by these criteria and the fitted median age of reaching puberty in relation to serum PFOA and PFOS concentrations measured when puberty status was assigned. For boys, there was a relationship of reduced odds of reached puberty (raised testosterone) with increasing PFOS (delay of 190 days between the highest and lowest quartile). For girls, higher concentrations of PFOA or PFOS were associated with reduced odds of postmenarche (130 and 138 days of delay, respectively). In conclusion, our study showed a later age of puberty in this population correlated with PFC concentrations.	●	●		●	●	●				-		B	-
563	ヒト（生殖毒性）	Lopez-Espinosa, M. J.; Mondal, D.; Armstrong, B. G.; Eskenazi, B.; Fletcher, T.	Perfluoroalkyl Substances, Sex Hormones, and Insulin-like Growth Factor-1 at 6-9 Years of Age: A Cross-Sectional Analysis within the C8 Health Project	2016	Environ Health Perspect. 2016 Aug;124(8):1269-75. doi: 10.1289/ehp.1509869. Epub 2016 Jan 22.	BACKGROUND: Exposure to some perfluoroalkyl substances (PFAS), such as perfluorohexane sulfonate (PFHxS), perfluorooctanoate (PFOA), perfluorooctane sulfonate (PFOS), and perfluorononanoic acid (PFNA), may alter levels of sex hormones and insulin-like growth factor-1 (IGF-1) in animals. Human studies on this topic are scarce, and none have been conducted in young children.OBJECTIVES: We investigated the relationship between levels of PFAS and estradiol, total testosterone, and IGF-1 in 2292 children (6-9 years of age) from the C8 Health Project who lived near a chemical plant in the Mid-Ohio Valley (USA) with local contamination from PFOA.METHODS: Serum samples were collected in 2005-2006 and analyzed for PFAS, sex hormones, and IGF-1. Results from regression models were expressed as the adjusted percentage difference (95% CI) per sex-specific interquartile range (IQR) increment of each PFAS serum concentration. Analyses by PFAS quartiles were also conducted.RESULTS: Median concentrations of PFHxS, PFOA, PFOS, and PFNA were 8, 35, 22, and 1.7 ng/mL in boys and 7, 30, 21, and 1.7 ng/mL in girls. In boys, PFOA concentrations were significantly associated with testosterone levels (-4.9%; 95 CI: -8.7, -0.8%); PFOS with estradiol (-4.0%; 95 CI: -7.7, -0.1%), testosterone (-5.8%; 95 CI: -9.4, -2.0%), and IGF-1 (-5.9%; 95 CI: -8.3, -3.3%); and PFNA with IGF-1 (-3.5%; 95 CI: -6.0, -1.0%). In girls, significant associations were found between PFOS and testosterone (-6.6%; 95 CI: -10.1, -2.8%) and IGF-1 (-5.6%; -8.2, -2.9%); and PFNA and IGF-1 (-3.8%; 95 CI: -6.4, -1.2%). In both sexes, the magnitudes of the associations decreased monotonically across quartiles for both testosterone and IGF-1 in relation to PFOS, and for IGF-1 and PFNA in girls.CONCLUSIONS: To our knowledge, this is the first study suggesting that PFAS are associated with lower levels of IGF-1 and sex hormones in young children.CITATION: Lopez-Espinosa MJ, Mondal D, Armstrong BG, Eskenazi B, Fletcher T. 2016 Perfluoroalkyl substances, sex hormones, and insulin-like growth factor-1 at 44721 years of age: a cross-sectional analysis within the C8 Health Project.	●	●		●	●	●			●	-		B	-
564	ヒト（生殖毒性）	Louis, GM; Sapra, K. J.; Barr, D. B.; Lu, Z.; Sundaram, R.	Preconception perfluoroalkyl and polyfluoroalkyl substances and incident pregnancy loss, LIFE Study	2016	Reprod Toxicol. 2016 Oct;65:11-17. doi: 10.1016/j.reprotox.2016.06.011. Epub 2016 Jun 16.	Equivocal findings are reported for perfluoroalkyl and polyfluoroalkyl substances (PFASs) and self-reported pregnancy loss. We prospectively assessed PFASs and pregnancy loss in a cohort comprising 501 couples recruited preconception and followed daily through 7 post-conception weeks. Seven PFASs were quantified: 2-N-ethyl-perfluorooctane sulfonamide acetate (Et-PFOSA-AcOH); 2-N-methyl-perfluorooctane sulfonamido acetate (Me-PFOSA-AcOH); perfluorodecanoate (PFDeA); perfluorononanoate (PFNA); perfluorooctane sulfonamide (PFOSA); perfluorooctane sulfonate (PFOS); and perfluorooctanoate (PFOA). Women used home pregnancy test kits. Loss denoted conversion from a positive to a negative pregnancy test, onset of menses or clinical confirmation (n=98; 28%). Chemicals were log transformed and rescaled by their standard deviations to estimate adjusted hazard ratios (HRs) and 0.95 confidence intervals. No significantly elevated HRs were observed for any PFASs suggesting no association with loss: Et-PFOSA-AcOH (1.04; 0.87, 1.23), Me-PFOSA-AcOH (0.79; 0.61, 1.00; p<0.05), PFDeA (0.83; 0.66, 1.04), PFNA (0.86; 0.70, 1.06), PFOSA (0.74; 0.50, 1.09), PFOS (0.81; 0.65, 1.00), and PFOA (0.93; 0.75, 1.16).	●	●	●	●						-		C	-
565	ヒト（生殖毒性）	Louis, G. M. B.; Peterson, C. M.; Chen, Z.; Hediger, M. L.; Croughan, M. S.; Sundaram, R.; Stanford, J. B.; Fujimoto, V. Y.; Varner, M. W.; Giudice, L. C.; Kennedy, A.; Sun, L.; Wu, Q.; Kannan, K.	Perfluorochemicals and endometriosis: The ENDO study	2012	Epidemiology. 2012 Nov;23(6):799-805. doi: 10.1097/EDE.0b013e31826cc0cf.	Background: Environmental chemicals may be associated with endometriosis. No published research has focused on the possible role of perfluorochemicals (PFCs) despite their widespread presence in human tissues. Methods: We formulated two samples. The first was an operative sample comprising 495 women aged 18-44 years scheduled for laparoscopy/laparotomy at one of 14 participating clinical sites in the Salt Lake City or San Francisco area, 2007-2009. The second was a population-based sample comprising 131 women matched to the operative sample on age and residence within a 50-mile radius of participating clinics. Interviews and anthropometric assessments were conducted at enrollment, along with blood collection for the analysis of nine PFCs, which were quantified using liquid chromatography-tandem mass spectrometry. Endometriosis was defined based on surgical visualization (in the operative sample) or magnetic resonance imaging (in the population sample). Using logistic regression, we estimated odds ratios (ORs) and 95% confidence intervals (CIs) for each PFC (log-transformed), adjusting for age and body mass index, and then parity. Results: Serum perfluorooctanoic acid (PFOA; OR = 1.89 [95% CI = 1.17-3.06]) and perfluorononanoic acid (2.20 [1.02-4.75]) were associated with endometriosis in the operative sample; findings were moderately attenuated with parity adjustment (1.62 [0.99-2.66] and 1.99 [0.91-4.33], respectively). Perfluorooctane sulfonic acid (1.86 [1.05-3.30]) and PFOA (2.58 [1.18-5.64]) increased the odds for moderate/severe endometriosis, although the odds were similarly attenuated with parity adjustment (OR = 1.50 and 1.86, respectively). Conclusions: Select PFCs were associated with an endometriosis diagnosis. These associations await corroboration.	●	●	●	●						-		C	-
566	ヒト（生殖毒性）	Lum, K. J.; Sundaram, R.; Barr, D. B.; Louis, T. A.; Buck Louis, G. M.	Perfluoroalkyl Chemicals, Menstrual Cycle Length, and Fecundity: Findings from a Prospective Pregnancy Study	2017	Epidemiology. 2017 Jan;28(1):90-98. doi: 10.1097/EDE.0000000000000552.	BACKGROUND: Perfluoroalkyl substances have been associated with changes in menstrual cycle characteristics and fecundity, when modeled separately. However, these outcomes are biologically related, and we evaluate their joint association with exposure to perfluoroalkyl substances.METHODS: We recruited 501 couples from Michigan and Texas in 2005-2009 upon their discontinuing contraception and followed them until pregnancy or 12 months of trying. Female partners provided a serum sample on enrollment and completed daily journals on menstruation, intercourse, and pregnancy test results. We measured seven perfluoroalkyl substances in serum using liquid chromatography-tandem mass spectrometry. We assessed the association between perfluoroalkyl substances and menstrual cycle length using accelerated failure time models and between perfluoroalkyl substances and fecundity using a Bayesian joint modeling approach to incorporate cycle length.RESULTS: Menstrual cycles were 0.03 longer comparing women in the second versus first tertile of perfluorodecanoate (PFDeA; acceleration factor [AF] = 1.03, 0.95 credible interval [CrI] = [1.00, 1.05]), but 0.02 shorter for women in the highest versus lowest tertile of perfluorooctanoic acid (PFOA; AF = 0.98, 0.95 CrI = [0.96, 1.00]). When accounting for cycle length, relevant covariates, and remaining perfluoroalkyl substances, the probability of pregnancy was lower for women in second versus first tertile of perfluorononanoate (PFNA; odds ratio [OR] = 0.6, 0.95 CrI = [0.4, 1.0]) although not when comparing the highest versus lowest (OR = 0.7, 0.95 CrI = [0.3, 1.1]) tertile.CONCLUSIONS: In this prospective cohort study, we observed associations between two perfluoroalkyl substances and menstrual cycle length changes, and between select perfluoroalkyl substances and diminished fecundity at some (but not all) concentrations.	●	●		●					●	-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ランク①	文献ランク②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
567	ヒト（生殖毒性）	Lyngsø, J.; Ramlau-Hansen, C. H.; Høyer, B. B.; Støvring, H.; Bonde, J. P.; Jönsson, B. A.; Lindh, C. H.; Pedersen, H. S.; Ludwicki, J. K.; Zviezdai, V.; Toft, G.	Menstrual cycle characteristics in fertile women from Greenland, Poland and Ukraine exposed to perfluorinated chemicals: a cross-sectional study	2014	Hum Reprod. 2014 Feb;29(2):359-67. doi: 10.1093/humrep/det390. Epub 2013 Oct 25.	Study question: Does perfluorooctane sulfonate (PFOS) and perfluorooctanate (PFOA) exposure disrupt the menstrual cyclicity? Summary answer: The female reproductive system may be sensitive to PFOA exposure, with longer menstrual cycle length at higher exposure. What is known already: PFOS and PFOA are persistent man-made chemicals. Experimental animal studies suggest they are reproductive toxicants but epidemiological findings are inconsistent. Study design, size, duration: A cross-sectional study including 1623 pregnant women from the INUENDO cohort enrolled during antenatal care visits between June 2002 and May 2004 in Greenland, Poland and Ukraine. Participants/materials, setting, methods: Information on menstrual cycle characteristics was obtained by questionnaires together with a blood sample from each pregnant woman. Serum concentrations of PFOS and PFOA were measured by liquid chromatography tandem mass spectrometry. Multiple imputations were performed to account for missing data. The association between PFOS/PFOA and menstrual cycle length (short cycle: ≤24 days, long cycle: ≥32 days) and irregularities (≥7 days in difference between cycles) was analyzed using logistic regression with tertiles of exposure. Estimates are given as adjusted odds ratios (ORs) with 95% confidence intervals (CIs). Main results and the role of chance: Higher exposure levels of PFOA were associated with longer menstrual cycles in pooled estimates of all three countries. Compared with women in the lowest exposure tertile, the adjusted OR of long cycles was 1.8 (95% CI: 1.0; 3.3) among women in the highest tertile of PFOA exposure. No significant associations were observed between PFOS exposure and menstrual cycle characteristics. However, we observed a tendency toward more irregular cycles with higher exposure to PFOS [OR 1.7 (95% CI: 0.8; 3.5)]. The overall response rate was 45.3% with considerable variation between countries (91.3% in Greenland, 69.1% in Poland and 26.3% in Ukraine). Limitations, reasons for caution: Possible limitations in our study include varying participation rates across countries; a selected study group overrepresenting the most fertile part of the population; retrospective information on menstrual cycle characteristics; the determination of cut-points for all three outcome variables; and lacking information on some determinants of menstrual cycle characteristics, such as stress, physical activity, chronic diseases and gynecological disorders, thus confounding cannot be excluded. Wider implications of the findings: The generalizability of the study results is restricted to fertile women who manage to conceive and women who do not use oral contraceptives when getting pregnant or within 2 months before getting pregnant. To our knowledge only one previous epidemiological study has addressed the possible association between perfluorinated chemical exposure and menstrual disturbances. Though pointing toward different disturbances in cyclicity, both studies suggest that exposure to PFOA may affect the female reproductive function. This study contributes to the limited knowledge on effects of exposure to PFOA and PFOS on female reproductive function and suggests that the female reproductive system may be affected by environmental exposure to PFOA. Study funding/competing interest(s): Supported by a scholarship from Aarhus University Research Foundation. The collection of questionnaire data and blood samples was part of the INUENDO project supported by The European Commission (Contract no. QLK4-CT-2001-00 202), www.inuendo.dk. The Ukrainian part of the study was possible by a grant from INTAS (project 012 2205). Determination of PFOA and PFOS in serum was part of the CLEAR study (www.inuendo.dk/clear) supported by the European Commission's 7th Framework Program (FP7-ENV-2008-1-226217). No conflict of interest declared.	●	●		●					-		B	-
568	ヒト（発生毒性）	Maekawa, R.; Ito, R.; Iwasaki, Y.; Saito, K.; Akutsu, K.; Takatori, S.; Ishii, R.; Kondo, F.; Arai, Y.; Ohgane, J.; Shiota, K.; Makino, T.; Sugino, N.	Evidence of exposure to chemicals and heavy metals during pregnancy in Japanese women	2017	Reprod Med Biol. 2017 Aug 18;16(4):337-348. doi: 10.1002/rmb2.12049. eCollection 2017 Oct.	Purpose: Prenatal exposure to environmental chemicals is a growing concern, because such exposures have been shown to be associated with various diseases. The levels of chemicals and heavy metals in maternal blood, cord blood, maternal urine and amniotic fluid in Japanese pregnant women were investigated.Methods: A total of 145 women, including 14 fetal growth restriction cases, were included in the present study. The levels of phthalates (di[2-ethylhexyl]phthalate and mono[2-ethylhexyl]phthalate), perfluorinated compounds (perfluorooctane sulfonate, perfluorohexanoic acid, perfluorooctanoic acid, and perfluorononanoic acid), pesticides (dimethylphosphate, dimethylthiophosphate, diethylphosphate, diethylthiophosphate, 3-phenoxybenzoic acid, and octachlorodipropyl ether), bisphenol A, nicotine (nicotine, nornicotine, cotinine, norcotinine, and trans-3'-hydroxycotinine), polybrominated diphenyl ethers, and heavy metals were measured. The relationship between fetal growth and the levels of chemicals and heavy metals were investigated.Results: Phthalates, perfluorinated compounds, pesticides, polybrominated diphenyl ethers, and heavy metals were detected in high frequency, whereas nicotine and bisphenol A were almost negative. Phthalates, perfluorinated compounds, and several heavy metals were transferred to the fetus. High perfluorononanoic acid levels in the maternal blood and cord blood, and low perfluorooctanoic acid level in the cord blood were significantly and negatively associated with fetal growth.Conclusions: The present study showed that pregnant women in Japan and their fetuses are exposed to a variety of chemicals and heavy metals.	●	●							-		B	-
569	ヒト（生殖毒性）	Maisonet, M.; Calafat, A. M.; Marcus, M.; Jaakkola, J. J.; Lashen, H.	Prenatal exposure to perfluoroalkyl acids and serum testosterone concentrations at 15 years of age in female ALSPAC study participants	2015	Environ Health Perspect. 2015 Dec;123(12):1325-30. doi: 10.1289/ehp.1408847. Epub 2015 Jun 2.	BACKGROUND: Exposure to perfluorooctane sulfonic acid (PFOS) or to perfluorooctanoic acid (PFOA) increases mouse and human peroxisome proliferator-activated receptor alpha (PPARα) subtype activity, which influences lipid metabolism. Because cholesterol is the substrate from which testosterone is synthesized, exposure to these substances has the potential to alter testosterone concentrations.OBJECTIVES: We explored associations of total testosterone and sex hormone-binding globulin (SHBG) concentrations at age 15 years with prenatal exposures to PFOS, PFOA, perfluorohexane sulfonic acid (PFHxS), and perfluorononanoic acid (PFNA) in females.METHODS: Prenatal concentrations of the perfluoroalkyl acids (PFAAs) were measured in serum collected from pregnant mothers at enrollment (1991-1992) in the Avon Longitudinal Study of Parents and Children (ALSPAC). The median gestational age when the maternal blood sample was obtained was 16 weeks (interquartile range, 44893 weeks). Total testosterone and SHBG concentrations were measured in serum obtained from their daughters at 15 years of age. Associations between prenatal PFAAs concentrations and reproductive outcomes were estimated using linear regression models (n = 72).RESULTS: Adjusted total testosterone concentrations were on average 0.18-nmol/L (95% CI: 0.01, 0.35) higher in daughters with prenatal PFOS in the upper concentration tertile compared with daughters with prenatal PFOS in the lower tertile. Adjusted total testosterone concentrations were also higher in daughters with prenatal concentrations of PFOA (β = 0.24; 0.95 CI: 0.05, 0.43) and PFHxS (β = 0.18; 0.95 CI: 0.00, 0.35) in the upper tertile compared with daughters with concentrations in the lower tertile. We did not find evidence of associations between PFNA and total testosterone or between any of the PFAAs and SHBG.CONCLUSIONS: Our findings were based on a small study sample and should be interpreted with caution. However, they suggest that prenatal exposure to some PFAAs may alter testosterone concentrations in females.	●	●		●					-		B	-
570	ヒト（生殖毒性）	Manzano-Salgado, C. B.; Casas, M.; Lopez-Espinosa, M. J.; Ballester, F.; Iñiguez, C.; Martinez, D.; Costa, O.; Santa-Marina, L.; Pereda-Pereda, E.; Schettgen, T.; Sunyer, J.; Vrijheid, M.	Prenatal exposure to perfluoroalkyl substances and birth outcomes in a Spanish birth cohort	2017	Environ Int. 2017 Nov;108:278-284. doi: 10.1016/j.envint.2017.09.006.	BACKGROUND: Prenatal perfluorooctanoate (PFOA) exposure has been associated with reduced birth weight but maternal glomerular filtration rate (GFR) may attenuate this association. Further, this association remains unclear for other perfluoroalkyl substances (PFAS), such as perfluorooctane sulfonate (PFOS), perfluorohexane sulfonate (PFHxS), and perfluorononanoate (PFNA). We estimated associations between prenatal PFAS exposure and birth outcomes, and the influence of GFR, in a Spanish birth cohort.METHODS: We measured PFHxS, PFOS, PFOA, and PFNA in 1st-trimester maternal plasma (years: 2003-2008) in 1202 mother-child pairs. Continuous birth outcomes included standardized weight, length, head circumference, and gestational age. Binary outcomes included low birth weight (LBW), small-for-gestational-age, and preterm birth. We calculated maternal GFR from plasma-creatinine measurements in the 1st-trimester of pregnancy (n=765) using the Cockcroft-Gault formula. We used mixed-effects linear and logistic models with region of residence as random effect and adjustment for maternal age, parity, pre-pregnancy BMI, and fish intake during pregnancy.RESULTS: Newborns in this study weighted on average 3263g and had a median gestational age of 39.8weeks. The most abundant PFAS were PFOS and PFOA (median: 6.05 and 2.35ng/mL, respectively). Overall, PFAS concentrations were not significantly associated to birth outcomes. PFOA, PFHxS, and PFNA showed weak, non-statistically significant associations with reduced birth weights ranging from 8.6g to 10.3g per doubling of exposure. Higher PFOS exposure was associated with an OR of 1.9 (95% CI: 0.98, 3.68) for LBW (similar in births-at-term) in boys. Maternal GFR did not confound the associations.CONCLUSIONS: In this study, PFAS showed little association with birth outcomes. Higher PFHxS, PFOA, and PFNA concentrations were non-significantly associated with reduced birth weight. The association between PFOS and LBW seemed to be sex-specific. Finally, maternal GFR measured early during pregnancy had little influence on the estimated associations.	●	●	●	●					-		B	-
571	ヒト（生殖毒性）	Manzano-Salgado, C. B.; Casas, M.; Lopez-Espinosa, M. J.; Ballester, F.; Iñiguez, C.; Martinez, D.; Romaguera, D.; Fernández-Barrés, S.; Santa-Marina, L.; Basterretxea, M.; Schettgen, T.; Valvi, D.; Vioque, J.; Sunyer, J.; Vrijheid, M.	Prenatal exposure to perfluoroalkyl substances and cardiometabolic risk in children from the Spanish INMA birth cohort study	2017	Environ Health Perspect. 2017 Sep 20;125(9):097018. doi: 10.1289/EHP1330.	BACKGROUND: Perfluoroalkyl substances (PFAS) may affect body mass index (BMI) and other components of cardiometabolic (CM) risk during childhood, but evidence is scarce and inconsistent.OBJECTIVES: We estimated associations between prenatal PFAS exposures and outcomes relevant to cardiometabolic risk, including a composite CM-risk score.METHODS: We measured perfluorohexanesulfonic acid (PFHxS), perfluorooctanesulfonic acid (PFOS), perfluorooctanoic acid (PFOA), and perfluorononanoic acid (PFNA) in maternal plasma (first trimester). We assessed weight gain from birth until 6 mo. At 4 and 7 y, we calculated the age- and sex-specificz-scores for BMI, waist circumference (WC), and blood pressure (BP) (n≈1,000). At age 4, we calculated the age-, sex-, and region-specificz-scores for cholesterol, triglycerides (TGs), high-density (HDL-C), and low-density lipoprotein cholesterol (LDL-C) (n=627). At age 4, we calculated a CM-risk score (n=386) as the sum of the individual age-, sex-, and region-specificz-scores for WC, BP, HDL-C, and TGs. We used the average between the negative of HDL-Cz-score and TGsz-score to give similar weight to lipids and the other components in the score. A higher score indicates a higher cardiometabolic risk at age 4.RESULTS: PFOS and PFOA were the most abundant PFAS (geometric mean: 5.8 and 2.32 ng/mL, respectively). In general, prenatal PFAS concentrations were not associated with individual outcomes or the combined CM-risk score. Exceptions were positive associations between prenatal PFHxS and TGsz-score [for a doubling of exposure, β=0.11; 0.95 confidence interval (CI): 0.01, 0.21], and between PFNA and the CM-risk score (β=0.60; 0.95 CI: 0.04, 1.16). There was not clear or consistent evidence of modification by sex.CONCLUSIONS: We observed little or no evidence of associations between low prenatal PFAS exposures and outcomes related to cardiometabolic risk in a cohort of Spanish children followed from birth until 7 y.	●	●	●	●					-	1	A	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ラン①抽出	文献ラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
572	ヒト（生殖毒性）	Marks, K. J.; Cutler, A. J.; Jeddy, Z.; Northstone, K.; Kato, K.; Hartman, T. J.	Maternal serum concentrations of perfluoroalkyl substances and birth size in British boys	2019	Int J Hyg Environ Health. 2019 Jun;222(5):889-895. doi: 10.1016/j.ijheh.2019.03.008. Epub 2019 Apr 9.	Per- and polyfluoroalkyl substances (PFAS) have been widely used in commercial and industrial manufacturing processes since the 1950s. Inverse associations between prenatal exposure to PFAS and birth size have been found in populations around the globe. This study examined the association of prenatal maternal serum concentrations of perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorohexane sulfonic acid (PFHxS), and perfluorononanoic acid (PFNA) and birth size in British boys. The study included 457 mother-son dyads participating in the Avon Longitudinal Study of Parents and Children (ALSPAC). Birth weight (g), crown to heel length (cm), and head circumference (cm) were collected at delivery. PFAS were detected in all maternal serum samples during pregnancy (median: 30 weeks gestation (interquartile range: 12-33)). Median concentrations (interquartile range) were 13.8 ng/mL (11.0, 17.7), 3.0 ng/mL (2.3, 3.8), 1.9 ng/mL (1.4, 2.5), and 0.4 ng/mL (0.3, 0.5) for PFOS, PFOA, PFHxS, and PFNA, respectively. In multivariable linear regression models, inverse associations were detected between PFOS (continuous) and birth weight (β = -8.50 g, 0.95 CI = -15.93, -1.07 g), crown to heel length (β = -0.04 cm, 0.95 CI = -0.08, -0.01 cm), and head circumference (β = -0.02 cm, 0.95 CI = -0.04, -0.002 cm). In conclusion, prenatal exposure to high levels of PFOS may be associated with reduced birth size in male infants.	●	●	●							-		B	-
573	ヒト（生殖毒性）	McCoy, J. A.; Bangma, J. T.; Reiner, J. L.; Bowden, J. A.; Schnorr, J.; Slowey, M.; O'Leary, T.; Guillette, L. J.; Parrott, B. B.	Associations between perfluorinated alkyl acids in blood and ovarian follicular fluid and ovarian function in women undergoing assisted reproductive treatment	2017	Sci Total Environ. 2017 Dec 15;605-606:9-17. doi: 10.1016/j.scitotenv.2017.06.137. Epub 2017 Jun 23.	Endocrine disrupting contaminants, in combination with other environmental variables, are associated with altered reproductive health. Assisted reproductive technology (ART) procedures offer valuable opportunities to explore the connections between environmental contaminants in the ovarian microenvironment and measures of fertility, including impaired responsiveness to gonadotropins. Here, we investigate an emerging class of environmental contaminants, the perfluorinated alkyl acids (PFAAs), to determine whether ovarian contaminant levels are associated with measures of ovarian responsiveness and fertility outcomes in a South Carolina population of women undergoing ART. Levels of PFAAs in plasma and follicular fluid samples collected from women undergoing ovarian stimulation were analyzed by liquid chromatography tandem mass spectrometry (LC-MS/MS). Six PFAAs were detected in both plasma and follicular fluid. PFAA concentrations in plasma correlate strongly to those detected in ovary and, with the exception of one compound, remain stable throughout ovarian stimulation. The concentration of PFHxS in follicular fluid inversely relates to baseline follicle counts. While no significant relationships were detected between ovarian response measures and PFAA concentrations, we identified a negative relationship between follicular fluid PFDA and PFuNA and blastocyst conversion rates. Our assessments indicate that plasma levels of PFAAs serve as a sound proxy of those in the ovarian compartment and that follicular fluid levels of specific PFAA compounds are inversely related to important clinical measures of reproductive health including baseline follicle count and post-fertilization success.	●	●								-		B	-
574	ヒト（発生毒性）	Minatoya, M.; Itoh, S.; Miyashita, C.; Araki, A.; Sasaki, S.; Miura, R.; Goudarzi, H.; Iwasaki, Y.; Kishi, R.	Association of prenatal exposure to perfluoroalkyl substances with cord blood adipokines and birth size: The Hokkaido Study on environment and children's health	2017	Environ Res. 2017 Jul;156:175-182. doi: 10.1016/j.envres.2017.03.033. Epub 2017 Mar 27.	Perfluoroalkyl substances (PFASs) are synthetic chemicals that persist in the environment and in humans. There is a possible association between prenatal PFASs exposure and both neonate adipokines and birth size, yet epidemiological studies are very limited. The objective of this study was to examine associations of prenatal exposure to PFASs with cord blood adipokines and birth size. We conducted birth cohort study, the Hokkaido Study. In this study, 168 mother-child pairs were included. Perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) in maternal blood were determined by liquid chromatography tandem mass spectrometry. Cord blood adiponectin and leptin levels were measured by ELISA and RIA, respectively. Birth weight and ponderal index (PI) were obtained from birth record. The median maternal PFOS and PFOA were 5.1 and 1.4ng/mL, respectively. The median total adiponectin and leptin levels were 19.4μg/mL and 6.2ng/mL, respectively. Adjusted linear regression analyses found that PFOS level was positively associated with total adiponectin levels (β =0.12, 0.95 CI:0.01, 0.22), contrary was negatively associated with PI (β=-2.25, 0.95 CI: -4.01, -0.50). PFOA level was negatively associated with birth weight (β=-197, 0.95 CI: -391, -3). Leptin levels were not associated with PFASs levels. PFOS and adiponectin levels showed marginal dose-response relationship and both PFOS and PFOA and birth size showed significant dose-response relationships. Results from this study suggested that prenatal PFASs exposure may alter cord blood adiponectin levels and may decrease birth size.	●	●		●						-		B	-
575	ヒト（生殖毒性）	Mitro, S. D.; Sagiv, S. K.; Fleisch, A. F.; Jaacks, L. M.; Williams, P. L.; Rifas-Shiman, S. L.; Calafat, A. M.; Hivert, M. F.; Oken, E.; James-Todd, T. M.	Pregnancy per- and polyfluoroalkyl substance concentrations and postpartum health in project viva: A prospective cohort	2020	J Clin Endocrinol Metab. 2020 Sep 1;105(9):e3415-e3426. doi: 10.1210/clinem/dgaa431.	Context: Per- and polyfluoroalkyl substances (PFAS) are environmental chemicals linked to weight gain and type 2 diabetes. Objective: We examined the extent to which PFAS plasma concentrations during pregnancy were associated with postpartum anthropometry and biomarkers. Design, patients, and measures: We studied women recruited between 1999 and 2002 in the Project Viva prospective cohort with pregnancy plasma concentrations of PFAS, including perfluorooctanesulfonic acid (PFOS), perfluorooctanoic acid (PFOA), and 2-(N-ethyl-perfluorooctane sulfonamide) acetic acid (EtFOSAA). Three-year postpartum anthropometry measurements were available from 786 to 801 women, blood pressure from 761 women, and blood biomarkers from 450 to 454 women. We used multivariable regression to evaluate the association of log2-transformed PFAS with postpartum anthropometry, blood pressure, and blood biomarkers (leptin, adiponectin, sex hormone binding globulin [SHBG], hemoglobin A1c, interleukin-6 [IL-6], C-reactive protein), adjusting for age, prepregnancy body mass index, marital status, race/ethnicity, education, income, smoking, parity, and breastfeeding history. Results: Pregnancy concentrations of certain PFAS were associated with greater adiposity (eg, 0.4 cm [95% confidence interval [95%CI]: -0.1, 0.9] greater waist circumference per doubling in EtFOSAA; 0.2 cm [95%CI: -0.1, 0.5] greater mid-upper arm circumference per doubling in PFOA; 1.2 mm [95%CI: 0.1, 2.2] thicker sum of subscapular and triceps skinfolds per doubling in PFOS) and higher systolic blood pressure (eg, 1.2 mm Hg [95%CI: 0.3, 2.2] per doubling in PFOS) at 3 years postpartum. Higher EtFOSAA concentrations were also associated with 10.8% higher IL-6 (95%CI: 3.3, 18.9) and 6.1% lower SHBG (95%CI: 0.7, 11.2) per doubling. Conclusions: Pregnancy concentrations of EtFOSAA, PFOS, and PFOA were associated with adverse postpartum cardiometabolic markers.	●	●								-		B	-
576	ヒト（発生毒性）	Mora, A. M.; Oken, E.; Rifas-Shiman, S. L.; Webster, T. F.; Gillman, M. W.; Calafat, A. M.; Ye, X.; Sagiv, S. K.	Prenatal exposure to perfluoroalkyl substances and adiposity in early and mid-childhood	2017	Environ Health Perspect. 2017 Mar;125(3):467-473. doi: 10.1289/EHP246. Epub 2016 Jun 28.	BACKGROUND: Few studies have examined whether prenatal exposure to perfluoroalkyl substances (PFASs) is associated with childhood adiposity.OBJECTIVE: We examined associations of prenatal exposure to PFASs with adiposity in early and mid-childhood.METHODS: We measured plasma PFAS concentrations in 1645 pregnant women (median, 9.6 weeks gestation) enrolled in Project Viva, a prospective pre-birth cohort study in Massachusetts (USA), between 1999 and 2002 We assessed overall and central adiposity in 1006 children in early childhood (median, 3.2 years) and 876 in mid-childhood (median, 7.7 years) using anthropometric and dual X-ray absorptiometry (DXA) measurements. We fitted multivariable linear regression models to estimate exposure-outcome associations and evaluated effect modification by child sex.RESULTS: Median (25-75th percentiles) prenatal plasma perfluorooctanoate (PFOA), perfluorooctane sulfonate (PFOS), perfluorohexane sulfonate (PFHxS), and perfluorononanoate (PFNA) concentrations in children assessed in early childhood were 5.6 (4.1-7.7), 24.8 (18.4-33.9), 2.4 (1.6-3.8), and 0.6 (0.5-0.9) ng/mL, respectively. Among girls, each interquartile range increment of prenatal PFOA concentrations was associated with 0.21 kg/m(2) (95% CI: -0.05, 0.48) higher body mass index, 0.76 mm (95% CI: -0.17, 1.70) higher sum of subscapular and triceps skinfold thickness, and 0.17 kg/m(2) (95% CI: -0.02, 0.36) higher DXA total fat mass index in mid-childhood. Similar associations were observed for PFOS, PFHxS, and PFNA. We observed null associations for boys and early-childhood adiposity measures.CONCLUSIONS: In this cohort, prenatal exposure to PFASs was associated with small increases in adiposity measurements in mid-childhood, but only among girls. Citation: Mora AM, Oken E, Rifas-Shiman SL, Webster TF, Gillman MW, Calafat AM, Ye X, Sagiv SK. 2017 Prenatal exposure to perfluoroalkyl substances and adiposity in early and mid-childhood.	●	●	●	●						-		B	-
577	ヒト（生殖毒性）	Ngueta, G.; Longnecker, M. P.; Yoon, M.; Ruark, C. D.; Clewell, H. J.; Andersen, M. E.; Verner, M. A.	Quantitative bias analysis of a reported association between perfluoroalkyl substances (PFAS) and endometriosis: The influence of oral contraceptive use	2017	Environ Int. 2017 Jul;104:118-121. doi: 10.1016/j.envint.2017.03.023. Epub 2017 Apr 6.	An association between serum levels of perfluoroalkyl substances (PFAS) and endometriosis has recently been reported in an epidemiologic study. Oral contraceptive use to treat dysmenorrhea (pelvic pain associated with endometriosis) could potentially influence this association by reducing menstrual fluid loss, a route of excretion for PFAS. In this study, we aimed to evaluate the influence of differential oral contraceptive use on the association between PFAS and endometriosis. We used a published life-stage physiologically based pharmacokinetic (PBPK) model to simulate plasma levels of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) from birth to age at study participation (range 18-44years). In the simulated population, PFAS level distributions matched those for controls in the epidemiologic study. Prevalence and geometric mean duration (standard deviation [SD]) of oral contraceptive use in the simulated women were based on data from the National Health and Nutrition Examination Survey; among the women with endometriosis the values were, respectively, 0.29 and 6.8 -3.1 years; among those without endometriosis these values were 0.18 and 5.3 -2.8 years. In simulations, menstrual fluid loss (ml/cycle) in women taking oral contraceptives was assumed to be 0.56 of loss in non-users. We evaluated the association between simulated plasma PFAS concentration and endometriosis in the simulated population using logistic regression. Based on the simulations, the association between PFAS levels and endometriosis attributable to differential contraceptive use had an odds ratio (95% CI) of 1.05 (1.02, 1.07) for a loge unit increase in PFOA and 1.03 (1.02, 1.05) for PFOS. In comparison, the epidemiologic study reported odds ratios of 1.62 (0.99, 2.66) for PFOA and 1.25 (0.87, 1.80) for PFOS. Our results suggest that the influence of oral contraceptive use on the association between PFAS levels and endometriosis is relatively small.	●	●		●						-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報収集対象抽出	文献ランク①	文献ランク②
578	ヒト（発生毒性）	Ode, A.; Källén, K.; Gustafsson, P.; Rylander, L.; Jönsson, B. A.; Olofsson, P.; Ivarsson, S. A.; Lindh, C. H.; Rignell-Hydbom, A.	Fetal exposure to perfluorinated compounds and attention deficit hyperactivity disorder in childhood	2014	PLoS One. 2014 Apr 23;9(4):e95891. doi: 10.1371/journal.pone.0095891. eCollection 2014.	BACKGROUND: The association between exposure to perfluorinated compounds (PFCs) and attention deficit hyperactivity disorder (ADHD) diagnosis has been sparsely investigated in humans and the findings are inconsistent.OBJECTIVES: A matched case-control study was conducted to investigate the association between fetal exposure to PFCs and ADHD diagnosis in childhood.METHODS: The study base comprised children born in Malmö, Sweden, between 1978 and 2000 that were followed up until 2005 Children with ADHD (n ＝ 206) were identified at the Department of Child and Adolescent Psychiatry. Controls (n ＝ 206) were selected from the study base and were matched for year of birth and maternal country of birth. PFC concentrations were measured in umbilical cord serum samples. The differences of the PFC concentrations between cases and controls were investigated using Wilcoxon's paired test. Possible threshold effects (above the upper quartile for perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) and above limit of detection [LOD] for perfluorononanoic acid (PFNA)) were evaluated by conditional logistic regression.RESULTS: The median umbilical cord serum concentrations of PFOS were 6.92 ng/ml in the cases and 6.77 ng/ml in the controls. The corresponding concentrations of PFOA were 1.8 and 1.83 ng/ml. No associations between PFCs and ADHD were observed. Odds ratios adjusted for smoking status, parity, and gestational age were 0.81 (95% confidence interval [CI] 0.5 to 1.32) for PFOS, 1.07 (95% CI 0.67 to 1.7) for PFOA, and 1.1 (95% CI 0.75 to 1.7) for PFNA.CONCLUSIONS: The current study revealed no support for an association between fetal exposure to PFOS, PFOA, or PFNA and ADHD.	●	●		●						-		B	-
579	ヒト（生殖毒性）	Olsen GW, Gilliland FD, Burlew MM, Burris JM, Mandel,JS, Mandel JH.	An epidemiologic investigation of reproductive hormones in men with occupational exposure to perfluorooctanoic acid	1998	J Occup Environ Med. 1998 Jul;40(7):614-22. doi: 10.1097/00043764-199807000-00006.	Perfluorooctanoic acid (PFOA), a potent synthetic surfactant used in industrial applications, is a peroxisome proliferator that has resulted in dose-related increases in hepatic, pancreatic acinar, and Leydig cell adenomas in laboratory animals. In addition, PFOA increased serum estradiol levels through the induction of hepatic aromatase activity. In 1993 and 1995, we conducted two cross-sectional studies of 111 and 80 production workers, respectively, and specifically measured their serum PFOA in relation to several reproductive hormones to determine whether such an effect occurs in humans. PFOA was not significantly associated with estradiol or testosterone in either year's study. A 0.1 increase in mean estradiol levels was observed among employees who had the highest levels of serum PFOA, although this association was confounded by body mass index. Neither was PFOA consistently associated with the other measured hormones. Our results provide reasonable assurance that, in this production setting, there were no significant hormonal changes associated with PFOA at the serum levels measured. Limitations of this investigation include its cross-sectional design, the few subjects exposed at the highest levels, and the lower levels of serum PFOA measured, compared with those levels reported to cause effects in laboratory animal studies.	●	●		●		●	●		●	-		C	-
580	ヒト（発生毒性）	Oulhote, Y.; Steuerwald, U.; Debes, F.; Weihe, P.; Grandjean, P.	Behavioral difficulties in 7-year old children in relation to developmental exposure to perfluorinated alkyl substances [Review]	2016	Environ Int. 2016 Dec;97:237-245. doi: 10.1016/j.envint.2016.09.015. Epub 2016 Sep 29.	BACKGROUND: Perfluorinated alkyl substances (PFAS) are suspected endocrine disruptors that are highly persistent and neurotoxic in animals. Human epidemiological studies of exposure-related deviations of children's behaviors are sparse. We assessed the associations between prenatal, 5- and 7-year PFAS exposures and behavioral problem scores in 7-year Faroese children.METHODS: Concentrations of perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), and perfluorodecanoic acid (PFDA), perfluorooctane sulfonate (PFOS), and perfluorohexane sulfonic acid (PFHxS) were measured in maternal serum and in serum from children at ages 5 and 7years (n=539, 508, and 491, respectively). We used multivariable regressions and structural equations models to estimate the covariate-adjusted associations between serum-PFAS concentrations and behavioral difficulties, as assessed by the strengths and difficulties questionnaire (SDQ) at age 7.RESULTS: Serum-PFOS and PFHxS concentrations declined over time, whereas PFOA, PFNA, and PFDA tended to increase. No associations were observed between prenatal PFAS concentrations and SDQ scores. However, a two-fold increase in 5-year serum-PFOA, PFNA, and PFDA concentrations was associated with increases in total SDQ scores by 1.03 (95% CI: 0.11, 1.95), 0.72 (95% CI: 0.07, 1.38) and 0.78 points (95% CI: 0.01, 1.55), respectively. For SDQ subscales, significant associations were found in regard to hyperactivity, peer relationship, and conduct problems, as well as internalizing and externalizing problems and autism screening composite scores. Cross-sectional analyses at age 7years showed possible sex-dimorphic associations between PFAS concentrations and SDQ scores, where girls had consistently positive associations with SDQ scores whereas boys exhibited a pattern of negative or null associations.CONCLUSIONS: Higher serum PFAS concentrations at ages 5- and 7-years, but not prenatally, were associated with parent-reported behavioral problems at age 7	●	●	●	●						-		B	-
581	ヒト（生殖毒性）	Pan, Y.; Cui, Q.; Wang, J.; Sheng, N.; Jing, J.; Yao, B.; Dai, J.	Profiles of Emerging and Legacy Per-/Polyfluoroalkyl Substances in Matched Serum and Semen Samples: New Implications for Human Semen Quality	2019	Environ Health Perspect. 2019 Dec;127(12):127005. doi: 10.1289/EHP4431. Epub 2019 Dec 16.	BACKGROUND: Epidemiological evidence remains equivocal on the associations between environmentally relevant levels of per-/polyfluoroalkyl substances (PFASs) and human semen quality.OBJECTIVES: We aimed to test whether the potential effects on semen quality could be better observed when seminal PFAS levels were used as an exposure marker compared with serum PFAS levels.METHODS: Matched semen and serum samples from 664 adult men were collected from a cross-sectional population in China from 2015 to 2016 Multiple semen parameters were assessed, along with measurement of 16 target PFASs in semen and serum. Partitioning between semen and serum was evaluated by the ratio of matrix-specific PFAS concentrations. Regression model results were expressed as the difference in each semen parameter associated with the per unit increase in the In-transformed PFAS level after adjusting for confounders.RESULTS: Perfluorooctanoate (PFOA), perfluorooctane sulfonate (PFOS), and emerging chlorinated polyfluorinated ether sulfonate (6:2 Cl-PFESA) were detected at their highest concentrations in both semen and serum, with median concentrations of 0.23, 0.10, and in semen, respectively, and a semen-to-serum ratio of 1.3:3.1. The between-matrix correlations of these PFAS concentrations were high (). Seminal PFOA, PFOS, and 6:2 Cl-PFESA levels were significantly associated with a lower percentage of progressive sperm and higher percentage of DNA fragmentation (false discovery rate-adjusted). Associations between serum PFAS levels and semen parameters were generally statistically weaker, except for DNA stainability, which was more strongly associated with serum-based PFASs than with semen-based PFASs.CONCLUSIONS: Our results suggest the potential for deleterious effects following exposure to 6:2 Cl-PFESA and other PFASs. Compared with serum PFAS levels, the much clearer association of seminal PFAS levels with semen parameters suggests its advantage in hazard assessment on semen quality, although the potential for confounding might be higher. Exposure measurements in target tissue may be critical in clarifying effects related to PFAS exposure.	●	●							●	-		B	-
582	ヒト（生殖毒性）	Petersen, M. S.; Halling, J.; J ørgensen, N.; Nielsen, F.; Grandjean, P.; Jensen, T. K.; Weihe, P.	Reproductive function in a population of young Faroese men with elevated exposure to polychlorinated biphenyls (pcbs) and perfluorinated alkylate substances (pfas)	2018	Int J Environ Res Public Health. 2018 Aug 30;15(9):1880. doi: 10.3390/ijerph15091880.	Semen quality may be adversely affected by exposure to environmental chemicals such as polychlorinated biphenyls (PCBs) and perfluorinated alkylate substances (PFASs) that are persistent and may act as endocrine disrupting compounds. The aim of this study was to explore whether PCBs or PFASs exposure were associated with abnormalities in semen quality or reproductive hormones in Faroese men. This population based cross-sectional study includes 263 Faroese men (24‐26 years) who delivered a semen sample for assessment of sperm concentration, total sperm count, semen volume, morphology and motility. A blood sample was drawn and analyzed for reproductive hormones, PCBs and PFASs. Exposure to ΣPCBs and perfluorooctane sulfonate (PFOS) was positively associated with sex hormone-binding globulin (SHBG) and luteinizing hormone (LH). In addition, total testosterone (T) was positively associated with ΣPCB. Both PCBs and PFOS appear to lead to increased SHBG, perhaps mediated via the liver. The higher total T associated with PCB may represent a compensatory adaption to elevated SHBG levels to maintain an unchanged free testosterone concentration. The positive association to LH for both PCBs and PFOS may indicate a direct adverse effect on the testosterone producing Leydig cells.	●	●							●	-		B	-
583	ヒト（生殖毒性）	Petro, E. M.; D'Hollander, W.; Covaci, A.; Bervoets, L.; Fransen, E.; De Neubourg, D.; De Pauw, I.; Leroy, J. L.; Jorssen, E. P.; Bols, P. E.	Perfluoroalkyl acid contamination of follicular fluid and its consequence for in vitro oocyte developmental competence	2014	Sci Total Environ. 2014 Oct 15;496:282-288. doi: 10.1016/j.scitotenv.2014.07.028. Epub 2014 Aug 2.	Perfluoroalkyl acids (PFAAs) have been shown to induce negative effects in laboratory animals and in vitro experiments. Also, PFAAs have been detected in human tissues and body fluids. The ovarian follicle constitutes a fragile micro-environment where interactions between hormones, growth factors, the oocyte and surrounding somatic cells are essential to generate a fully competent oocyte. In vitro experiments suggest that PFAAs can influence this balance, but very scarce in vivo data are available to confirm this assumption. In fact, the potential PFAA-presence in the follicular micro-environment is currently unknown. Therefore, we investigated if PFAAs are present in human follicular fluid and if their presence could be a risk factor for in vivo exposed developing oocytes. Furthermore, we compared the PFAA-distribution within serum and follicular fluid. PFAAs were analyzed by LC/MS in follicular fluid (n=38) and serum (n=20) samples from women undergoing assisted reproductive technologies (ARTs). Statistical models were used to investigate PFAA-distribution in both body fluids, to compare this behavior with the distribution of lipophilic organic pollutants and to explore the relationship between patient characteristics, ART-results and follicular fluid contamination. Perfluorooctane sulfonate (PFOS) was the PFAA found in the highest concentration in follicular fluid [7.5 (0.1-30.4) ng/mL] and serum [7.6 (2.8-12.5) ng/mL]. A new variable, Principal Component 1, representing the overall PFAA-contamination of the follicular fluid samples, was associated with a higher fertilization rate (p<0.05) and a higher proportion of top embryos relative to the amount of retrieved oocytes (p<0.05), after adjusting for age, estradiol-concentration, BMI, male subfertility and the presence of other organic pollutants as explanatory variables. To conclude, overall higher PFAA-contamination in the follicular micro-environment was associated with a higher chance of an oocyte to develop into a high quality embryo. Also, PFAAs have different distribution patterns between serum and follicular fluid compared to the lipophilic organic pollutants. Further research is of course crucial to confirm these new observations.	●	●								-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ランク①	文献ランク②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
584	ヒト（発生毒性）	Quaak, Ilona; de Cock, Marijke; de Boer, Michiel; Lamoree, Marja; Leonards, Pim; van de Bor, Margot	Prenatal Exposure to Perfluoroalkyl Substances and Behavioral Development in Children	2016	Int J Environ Res Public Health. 2016 May 19;13(5):511. doi: 10.3390/ijerph13050511.	BACKGROUND: In recent years, prevalence rates of behavioral disorders in children have increased. One factor possibly implied in the etiology of behavioral disorders is exposure to perfluoroalkyl substances (PFASs). The use of PFASs is highly integrated into everyday life, and exposure is ubiquitous. Exposure to PFASs during early life may be particularly harmful, as it represents a critical time window for brain development. However, research in the area is limited, especially among preschool children. The objective of the current study was to explore the relationship between prenatal exposure to several PFASs and behavioral development at the age of 18 months. METHODS: Data from the Dutch cohort LINC (Linking Maternal Nutrition to Child Health) were used. Perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) were measured in cord plasma. The total exposure of PFASs was also calculated (ΣPFASs). Behavioral development was assessed with the Child Behavior Checklist 1.5-5 (CBCL 1.5-5). The CBCL scales "Attention Deficit Hyperactivity Disorder" (ADHD) and "Externalizing problems" were used for further analysis. Separate regression models were composed for each combination, in which exposure levels were classified in tertiles. Both whole population and sex-stratified analyses were performed. A family history of ADHD, the educational level, smoking or using alcohol or illicit drugs during pregnancy were considered as confounders. In total, data from 76 mother-child pairs was included. RESULTS: No significant associations were found between prenatal PFAS exposure and ADHD scores in the whole population and in the sex-stratified analyses. With regard to externalizing behavior, a significant negative association was found between the highest levels of ΣPFAS exposure and externalizing problem behavior in the whole population, but only in the crude model. After stratifying for sex, boys in the second and third tertile of exposure to PFOA presented significantly lower scores on the Externalizing Problem Scale than boys with the lowest exposure levels in the adjusted model. Girls exposed to higher levels of ΣPFAS exposure (T2) showed significantly lower scores on the Externalizing Problem Scale, in both crude and adjusted models. No significant associations with PFOS were found. CONCLUSIONS: RESULTS from the current study show that prenatal exposure to PFOA was negatively related to externalizing behavior in boys. RESULTS were different for boys and girls, emphasizing that mechanisms at work might be sex-dependent. However, results should be interpreted with caution as the sample size was small. whole population and in the sex-stratified analyses. With regard to externalizing behavior, a significant negative association was found between the highest levels of ΣPFAS exposure and externalizing problem behavior in the whole population, but only in the crude model. After stratifying for sex, boys in the second and third tertile of exposure to PFOA presented significantly lower scores on the Externalizing Problem Scale than boys with the lowest exposure levels in the adjusted model. Girls exposed to higher levels of ΣPFAS exposure (T2) showed significantly lower scores on the Externalizing Problem Scale, in both crude and adjusted models. No significant associations with PFOS were found. CONCLUSIONS: RESULTS from the current study show that prenatal exposure to PFOA was negatively related to externalizing behavior in boys. RESULTS were different for boys and girls, emphasizing that mechanisms at work might be sex-dependent. However, results should be interpreted with caution as the sample size was small.	●	●	●	●						-		B	-
585	ヒト（生殖毒性）	Rokoff, L. B.; Rifas-Shiman, S. L.; Coull, B. A.; Cardenas, A.; Calafat, A. M.; Ye, X.; Gryparis, A.; Schwartz, J.; Sagiv, S. K.; Gold, D. R.; Oken, E.; Fleisch, A. F.	Cumulative exposure to environmental pollutants during early pregnancy and reduced fetal growth: the Project Viva cohort	2018	Environ Health. 2018 Feb 20;17(1):19. doi: 10.1186/s12940-018-0363-4.	BACKGROUND: Reduced fetal growth is associated with perinatal and later morbidity. Prenatal exposure to environmental pollutants is linked to reduced fetal growth at birth, but the impact of concomitant exposure to multiple pollutants is unclear. The purpose of this study was to examine interactions between early pregnancy exposure to cigarette smoke, traffic pollution, and select perfluoroalkyl substances (PFASs) on birth weight-for-gestational age (BW/GA).METHODS: Among 1597 Project Viva mother-infant pairs, we assessed maternal cigarette smoking by questionnaire, traffic pollution at residential address by black carbon land use regression model, and plasma concentration of select PFASs in early pregnancy. We calculated sex-specific BW/GA z-scores, an index of fetal growth, from national reference data. We fit covariate-adjusted multi-pollutant linear regression models and examined interactions between exposures, using a likelihood-ratio test to identify a best-fit model.RESULTS: Two hundred six -0.13 mothers smoked during pregnancy. Mean [standard deviation (SD)] for black carbon was 0.8 -0.3 μg/m3, perfluorooctane sulfonate (PFOS) was 29.1 -16.5 ng/mL, and BW/GA z-score was 0.19 (0.96). In the best-fit model, BW/GA z-score was lower in infants of mothers exposed to greater black carbon [- 0.08 (95% CI: -0.15, - 0.01) per interquartile range (IQR)]. BW/GA z-score (95% CI) was also lower in infants of mothers who smoked [- 0.09 (- 0.23, 0.06)] or were exposed to greater PFOS [- 0.03 (- 0.07, 0.02) per IQR], although confidence intervals crossed the null. There were no interactions between exposures. In secondary analyses, instead of PFOS, we examined perfluorononanoate (PFNA) [mean (SD): 0.7 -0.4 ng/mL], a PFAS more closely linked to lower BW/GA in our cohort. The best-fit multi-pollutant model included positive two-way interactions between PFNA and both black carbon and smoking (p-interactions = 0.03).CONCLUSIONS: Concurrent prenatal exposures to maternal smoking, black carbon, and PFOS are additively associated with lower fetal growth, whereas PFNA may attenuate associations of smoking and black carbon with lower fetal growth. It is important to examine interactions between multiple exposures in relation to health outcomes, as effects may not always be additive and may shed light on biological pathways.	●	●								-		1	A	-
586	ヒト（生殖毒性）	Romano, M. E.; Xu, Y.; Calafat, A. M.; Yolton, K.; Chen, A.; Webster, G. M.; Eliot, M. N.; Howard, C. R.; Lanphear, B. P.; Braun, J. M.	Maternal serum perfluoroalkyl substances during pregnancy and duration of breastfeeding	2016	Environ Res. 2016 Aug;149:239-246. doi: 10.1016/j.envres.2016.04.034. Epub 2016 May 11.	BACKGROUND: Perfluoroalkyl substances (PFAS) may affect breast development and decrease duration of breastfeeding, thus interfering with the health benefits of breastfeeding. We investigated the association between maternal PFAS exposure and breastfeeding duration.METHODS: We measured PFAS concentrations in maternal serum collected during pregnancy in 2003-2006. After delivery, women (n=336) completed standardized breastfeeding surveys every 3 months until ending breastfeeding or 36 months postpartum. We estimated relative risks (RRs) for ending any breastfeeding within 44626 months postpartum by Poisson regression, adjusted for relevant confounding factors.RESULTS: Women in the 4th quartile of perfluorooctanoic acid (PFOA) serum concentration had 1.77 times the risk of ending any breastfeeding by 3 months (95% confidence interval (CI): 1.23, 2.54; p-trend=0.003) and 1.41 times the risk of ending any breastfeeding by 6 months (95%CI: 1.06, 1.87; p-trend=0.038), compared with women in the first quartile. Women in the 4th quartile of perfluorooctane sulfonic acid serum concentration had a marginally increased risk of discontinuing any breastfeeding by 3 months (RR=1.32; 95%CI: 0.97, 1.79; p-trend=0.065).CONCLUSIONS: Maternal serum PFOA concentrations were inversely related to duration of any breastfeeding in this cohort, even after controlling for prior breastfeeding. These findings suggest that PFOA exposure may adversely affect breastfeeding duration and highlight the need to consider the potential adverse effects of maternal environmental chemical exposure on breastfeeding.	●	●		●		●				-		C	-
587	ヒト（生殖毒性）	Ruark, C. D.; Song, G.; Yoon, M.; Verner, M. A.; Andersen, M. E.; Clewell, H. J.; Longnecker, M. P.	Quantitative bias analysis for epidemiological associations of perfluoroalkyl substance serum concentrations and early onset of menopause	2017	Environ Int. 2017 Feb;99:245-254. doi: 10.1016/j.envint.2016.11.030. Epub 2016 Dec 5.	An association between increased serum concentrations of perfluoroalkyl substances (PFAS) such as perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) and early menopause has been reported (Knox et al., 2011; Taylor et al., 2014). This association may be explained by the fact that women who underwent menopause no longer excrete PFAS through menstruation. Our objective was to assess how much of the epidemiologic association between PFAS and altered timing of menopause might be explained by reverse causality. We extended a published population life-stage physiologically-based pharmacokinetic (PBPK) model of PFOS and PFOA characterized by realistic distributions of physiological parameters including age at menopause. We then conducted Monte Carlo simulations to replicate the Taylor population (Taylor et al., 2014) and the Knox population (Knox et al., 2011). The analysis of the simulated data overall showed a pattern of results that was comparable to those reported in epidemiological studies. For example, in the simulated Knox population (ages 42-51) the odds ratio (OR) for menopause in the fifth quintile of PFOA compared to those in the first quintile was 1.33 (95% CI 1.26-1.40), whereas the reported OR was 1.4 (95% CI 1.1-1.8). Using our model structure, a substantial portion of the associations reported can be explained by pharmacokinetics.	●	●		●						-		C	-
588	ヒト（生殖毒性）	Rylander, L.; Lindh, C. H.; Hansson, , S. R.; Broberg, K.; Källén, K.	Per- and polyfluoroalkyl substances in early pregnancy and risk for preeclampsia: a case-control study in Southern Sweden	2020	Toxics. 2020 Jun 16;8(2):43. doi: 10.3390/toxics8020043.	Preeclampsia is one of the most common causes of perinatal and maternal morbidity/mortality. One suggested environmental risk factor is exposure to endocrine-disrupting pollutants such as per- and polyfluoroalkyl substances (PFAS). The present case-control study in southern Sweden aims to investigate the hypothesized association between serum concentrations of PFAS in early pregnancy and the risk of developing preeclampsia. The study included 296 women diagnosed with preeclampsia (cases) and 580 healthy pregnant women (controls). Maternal serum samples were obtained from a biobank of samples collected in early pregnancy in connection with screening for infections. Serum concentrations of perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), perfluorononanoic acid (PFNA), and perfluorohexane sulfonate (PFHxS) were analyzed using liquid chromatography-tandem-mass-spectrometry (LC/MS/MS). Among primiparous women, there were no differences in PFAS concentrations in early pregnancy between the cases and the controls whereas among multipara women, the cases had significantly higher concentrations of PFNA (median concentrations were 0.44 and 0.38 ng/mL, p = 0.04). When individual PFAS were categorized into quartiles and adjustment for potential confounders was performed, the women in the highest quartiles had no significant increased risks of developing preeclampsia as compared with women in the lowest category. In conclusion, the present study provides limited support for the hypothesized association between PFAS and preeclampsia in a population with relatively low exposure levels.	●	●								-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
589	ヒト（生殖毒性）	Šabović, I.; Cosci, I.; De Toni, L.; Ferramosca, A.; Stornaiuolo, M.; Di Nisio, A.; Dall'Acqua, S.; Garolla, A.; Foresta, C.	Perfluoro-octanoic acid impairs sperm motility through the alteration of plasma membrane	2019	J Endocrinol Invest. 2020 May;43(5):641-652. doi: 10.1007/s40618-019-01152-0. Epub 2019 Nov 27.	Context: Perfluoroalkyl-substances (PFAS) are chemical additives considered harmful for humans. We recently showed that accumulation of perfluoro-octanoic acid (PFOA) in human semen of exposed subjects was associated with altered motility parameters of sperm cells, suggesting direct toxicity. Objectives: To determine whether direct exposure of human spermatozoa to PFOA was associated to impairment of cell function. Patients and methods: Spermatozoa isolated from semen samples of ten normozoospermic healthy donors were exposed up to 2 h to PFOA, at concentrations from 0.1 to 10 ng/mL. Viability and motility parameters were evaluated by Sperm Class Analyser. Cell respiratory function was assessed by both mitochondrial probe JC-1 and respiratory control ratio (RCR) determination. Sperm accumulation of PFOA was quantified by liquid chromatography-mass spectrometry. Expression of organic ion-transporters OATP1 and SLCO1B2 was assessed by immunofluorescence and respective role in PFOA accumulation was evaluated by either blockade with probenecid or membrane scavenging through β-cyclodextrin (β-CD). Plasma membrane fluidity and electrochemical potential (ΔΨp) were evaluated, respectively, with Merocyanine-540 and Di-3-ANEPPDHQ fluorescent probes. Results: Compared to untreated controls, a threefold increase of the percentage of non-motile sperms was observed after 2 h of exposure to PFOA regardless of the concentration of PFOA, whilst RCR was significantly reduced. Only scavenging with β-CD was effective in reducing PFOA accumulation, suggesting membrane involvement. Altered membrane fluidity, reduced ΔΨp and sperm motility loss associated with exposure to PFOA were reverted by β-CD treatment. Conclusion: PFOA alters human sperm motility through plasma-membrane disruption, an effect recovered by incubation with β-CD.	●	●							-		C	-
590	ヒト（生殖毒性）	Sagiv, S. K.; Rifas-Shiman, S. L.; Fleisch, A. F.; Webster, T. F.; Calafat, A. M.; Ye, X.; Gillman, M. W.; Oken, E.	Early Pregnancy Perfluoroalkyl Substance Plasma Concentrations and Birth Outcomes in Project Viva: Confounded by Pregnancy Hemodynamics? Am J Epidemiol 187: 793-802	2018	Am J Epidemiol. 2018 Apr 1;187(4):793-802. doi: 10.1093/aje/kwx332.	Associations of prenatal exposure to perfluoroalkyl substances (PFASs), ubiquitous chemicals used in stain and water resistant products, with adverse birth outcomes may be confounded by pregnancy hemodynamics. We measured plasma concentrations of four PFASs in early pregnancy (median, 9 weeks) among 1645 women in Project Viva, a Boston-area cohort recruited 1999-2002. We fit multivariable models to estimate PFAS associations with birth weight-for-gestational age z score and gestation length adjusting for sociodemographic confounders and two hemodynamic markers: 1) plasma albumin, a measure of plasma volume expansion, and 2) plasma creatinine, used to estimate glomerular filtration rate. Perfluorooctane sulfonate (PFOS) and perfluorononanoate (PFNA) were weakly inversely associated with birth weight-for-gestational age z scores (adjusted β = -0.04 (95% confidence interval (CI): -0.08, 0.1) and -0.06 (95% CI: -0.11, -0.01) per interquartile increase, respectively). PFOS and PFNA were also associated with higher odds of preterm birth (e.g., highest vs. lowest PFOS quartile adjusted odds ratio = 2.4 (95% CI: 1.3, 4.4)). Adjusting for markers of pregnancy hemodynamics (glomerular filtration rate and plasma albumin), to the extent that they accurately reflect underlying pregnancy physiology, did not materially impact associations. These results suggest that pregnancy hemodynamics may not confound associations with birth outcomes when PFASs are measured early in pregnancy.	●	●		●				●	-		B	-
591	ヒト（生殖毒性）	591_Savitz, DA; Stein, CR; Bartell, SM; Elston, B; Gong, J; Shin, HM; Wellenius, GA.	Perfluorooctanoic acid exposure and pregnancy outcome in a highly exposed community	2012	Epidemiology. 2012 May;23(3):386-92. doi: 10.1097/EDE.0b013e31824cb93b.	BACKGROUND: We assessed the association between perfluorooctanoic acid (PFOA) and pregnancy outcome in an area with elevated exposure to PFOA from drinking water contaminated by chemical plant releases. METHODS: Serum PFOA was measured, and reproductive and residential histories were obtained during 2005-2006. We estimated serum PFOA levels at the time of pregnancy for 11,737 pregnancies occurring between 1990 and 2006, based on historical information on PFOA releases, environmental distribution, pharmacokinetic modeling, and residential histories. We assessed the association between PFOA and the odds of miscarriage, stillbirth, preeclampsia, preterm birth, term low birthweight, and birth defects, controlling for calendar time, age, parity, education, and smoking. PFOA exposure was evaluated as a continuous measure (with and without log transformation) and in quintiles, combining the lowest 2 quintiles (< 6.8 ng/mL) as the referent. RESULTS: Measures of association between PFOA and miscarriage, preterm birth, term low birthweight, and birth defects were close to the null. Odds of stillbirth were elevated in the fourth quintile only. For preeclampsia, the odds ratio was 1.13 (95% confidence interval = 1.00-1.28) for an interquartile shift in log-transformed PFOA, and the odds ratios were 1.1-1.2 across the upper 3 quintiles of exposure. CONCLUSIONS: In this large, population-based study in a region with markedly elevated PFOA exposure, we found no associations between estimated serum PFOA levels and adverse pregnancy outcomes other than possibly preeclampsia. Conclusions are tempered by inherent limitations in exposure reconstruction and self-reported pregnancy outcome information.	●	●		●		●	●		-		C	-
592	ヒト（生殖毒性）	Savitz, D. A.; Stein, C. R.; Elston, B.; Wellenius, G. A.; Bartell, S. M.; Shin, H. M.; Vieira, V. M.; Fletcher, T.	Relationship of perfluorooctanoic Acid exposure to pregnancy outcome based on birth records in the mid-ohio valley	2012	Environ Health Perspect. 2012 Aug;120(8):1201-7. doi: 10.1289/ehp.1104752. Epub 2012 Mar 26.	Background: Perfluorooctanoic acid (PFOA) is a potential cause of adverse pregnancy outcomes, but previous studies have been limited by low exposures and small study size.Objectives: Using birth certificate information, we examined the relation between estimated PFOA exposure and birth outcomes in an area of West Virginia and Ohio whose drinking water was contaminated by a chemical plant.Methods: Births in the study area from 1990 through 2004 were examined to generate case groups of stillbirth (n = 106), pregnancy-induced hypertension (n = 224), preterm birth (n = 3,613), term low birth weight (n = 918), term small-for-gestational-age (SGA) (n = 353), and a continuous measure of birth weight among a sample of term births (n = 4,534). A 0.1 sample of term births ≥ 2500 g were selected as a source of controls (n = 3,616). Historical estimates of serum PFOA were derived from a previously developed fate and transport model. In a second study, we examined 4547 area births linked to a survey with residential history data.Results: In the analysis based only on birth records, we found no consistent evidence of an association between estimated PFOA exposure and stillbirth, pregnancy-induced hypertension, preterm birth, or indices of fetal growth. In the analysis of birth records linked to the survey, PFOA was unrelated to pregnancy-induced hypertension or preterm birth but showed some suggestion of an association with early preterm birth. Measures of growth restriction showed weak and inconsistent associations with PFOA.Conclusions: Based on the analysis using the health survey, these results provide little support for an effect of PFOA exposure on most pregnancy outcomes, except for early preterm birth and possibly fetal growth restriction.	●	●		●		●	●		-		C	-
593	ヒト（発生毒性）	Scinicariello, F.; Buser, M. C.; Abadin, H. G.; Attanasio, R.	Perfluoroalkyl substances and anthropomorphic measures in children (ages 3-11 years), NHANES 2013-2014	2020	Environ Res. 2020 Jul;186:109518. doi: 10.1016/j.envres.2020.109518. Epub 2020 Apr 15.	BACKGROUND: Perfluoroalkyl acids (PFAAs) are man-made compounds that are persistent in the environment and highly bioaccumulative in the body. Humans are exposed to a mixture of these substances, and the effects of these mixtures may be different than the effects noted for individual compounds. Prenatal exposure to PFAAs has been associated with decreased birth weight. The objective of the present study is to evaluate concurrent serum PFAA levels, as single compounds and as mixtures, in relation to anthropomorphic measures in children.METHODS: Using multivariate linear regression, we evaluated the association between single or PFAA mixtures and with height-for-age (HAZ), weight-for-age (WAZ), and BMI (BMIZ) z-scores in children (ages 3-11 years) participants of the National Health and Nutrition Examination Survey (NHANES) 2013-2014. Analyses were also stratified by sex. The PFAA mixture was based on relative potency factors express in terms of PFOA equivalency (CmixRPFi) or as molar sum of the PFAA congeners (∑molPFAA).RESULTS: There was a statistically significant association of PFHxS and PFOS with decreased HAZ in boys. The significantly decreased HAZ in boys was also found when the PFAAs were analyzed as mixtures: CmixRPFi (β = -0.33; 95%CI: 0.63, -0.04) or ΣmolPFAAs (β = -0.30; 95%CI: 0.56, -0.04). In boys, PFHxS was also associated with decreased WAZ and BMIZ. The only statistically significant association found in girls was between decreased HAZ and PFHxS.CONCLUSIONS: We found sex differences in the association between concurrent serum PFAA levels and anthropomorphic measures in children 3-11 years old. PFAA levels, as single congeners or as mixture concentrations were associated with decreased height-for-age z-score in boys.	●	●							-		B	-
594	ヒト（生殖毒性）	Shi, Y.; Yang, L.; Li, J.; Lai, J.; Wang, Y.; Zhao, Y.; Wu, Y.	Occurrence of perfluoroalkyl substances in cord serum and association with growth indicators in newborns from Beijing	2017	Chemosphere. 2017 Feb;169:396-402. doi: 10.1016/j.chemosphere.2016.11.050. Epub 2016 Nov 23.	Perfluoroalkyl substances (PFASs), a group of environmental pollutants, persistently exist in the environment. To investigate the associations between PFASs levels in cord serum and birth weight, birth length and ponderal index, we measured PFASs in cord serum samples from 170 infants from Feb. 2012 to Jun. 2012 in Beijing, China. The mean concentrations in cord serum samples for perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorohexane sulfonic acid (PFHxS), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA) and perfluoroundecanoic acid (PFUnA) were 1.285 ng/mL, 1.228 ng/mL, 0.230 ng/mL, 0.224 ng/mL, 0.100 ng/mL and 0.085 ng/mL, respectively. First-born children had slightly higher exposure levels of PFHxS (p < 0.001) and PFOA (p = 0.03) than second-born or third-born children. The spearman correlation coefficients with gestation time were individually 0.16 (p = 0.038) for PFHxS and 0.202 (p = 0.008) for PFOA. Both univariate and multivariate linear regression analysis showed that the exposure levels of PFASs had no statistically significant associations with birth weight, birth length or ponderal index in the present population. For male infants, we observed that PFHxS positively correlated with birth length, but the levels of PFUnA were negatively associated with birth length.	●	●	●	●			●		-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報抽出対象	文献ランク①	文献ランク②
595	ヒト（発生毒性）	Shoaff, J.; Papandonatos, G. D.; Calafat, A. M.; Chen, A.; Lanphear, B. P.; Ehrlich, S.; Kelsey, K. T.; Braun, J. M.	Prenatal exposure to perfluoroalkyl substances: Infant birth weight and early life growth	2018	Environ Epidemiol. 2018 Jun;2(2):e010. doi: 10.1097/EE9.0000000000000010.	Background: Prenatal perfluoroalkyl substance (PFAS) exposure has been associated with reduced birth weight and excess child adiposity, but the relationship between PFAS and early life growth is unknown. Objective: To determine if prenatal PFAS exposure was associated with birth weight, body composition and growth until 2 years of age. Methods: In a prospective cohort of women and their children from Cincinnati, OH, we quantified perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorononanoic acid (PFNA), and perfluorohexane sulfonic acid (PFHxS) in pregnant women's serum. We used linear regression to estimate associations of PFAS with birth weight z-scores (n=345) and linear mixed models to estimate associations with repeated weight and length/height measurements (n=334) at ages 4 weeks and 1 and 2 years, after adjusting for sociodemographic, perinatal, nutritional, and environmental factors. Results: We found non-significant inverse associations between PFAS and infant birth weight. For example, each log2 increase in PFOA was associated with a 0.03 standard deviation reduction in birth weight z-score (95% CI:-0.17, 0.10). Compared to associations with birth weight, we observed stronger associations between PFAS and child anthropometry from 4 weeks to 2 years. For instance, each log2 increase in PFOA was associated with a 0.12 standard deviation decrease in BMI z-score (95% CI: -0.25, 0.01). We did not observe any differences in growth rate associated with PFAS. Conclusion: We observed inverse associations between prenatal serum PFAS concentrations and anthropometry until age 2 years. Prenatal serum PFAS concentrations were not associated with growth rate in the first 2 years of life.	●	●								-		B	-
596	ヒト（発生毒性）	Souza, M. C. O.; Saraiva, M. C. P.; Honda, M.; Barbieri, M. A.; Bettiol, H.; Barbosa, F.; Kannan, K.	Exposure to per- and polyfluorinated alkyl substances in pregnant Brazilian women and its association with fetal growth	2020	Environ Res. 2020 Aug;187:109585. doi: 10.1016/j.envres.2020.109585. Epub 2020 Apr 28.	Research pertaining to exposure of humans to per- and polyfluorinated alkyl substances (PFASs) has received considerable public and regulatory attention in recent years. Although several studies have reported exposure to PFASs by populations in North America and western Europe, such information is still scarce in Latin America, including Brazil. In this study, concentrations of thirteen PFASs were determined in whole blood collected during the second trimester from 252 pregnant Brazilian women. This is a nested case-control study within the Brazilian Ribeirao Preto and Sao Luiz Birth Cohort Study (BRISA) with selected birth outcomes cases (n = 63) and matched controls (n = 189). PFASs concentrations were associated with conditions including preeclampsia, birth weight (BW), preterm birth, and intrauterine growth restriction (IUGR). Among PFASs measured, perfluorooctane sulfonate (PFOS) was found at the highest concentration (range: 1.06-106 ng mL-1 with a median value of 3.41 ng mL-1) which was followed by perfluorooctanoic acid (PFOA, range: 0.11-2.77 ng mL-1 with a median value of 0.20 ng mL-1). A significant positive association of PFOS and PFOA concentrations with fetal growth restriction (p < 0.05) was found. This is the first study to assess whole blood concentrations of PFASs and their effect on fetal growth in pregnant Brazilian women.	●	●								-		B	-
597	ヒト（生殖毒性）	Starling, A. P.; Adgate, J. L.; Hamman, R. F.; Kechris, K.; Calafat, A. M.; Dabelea, D.	Prenatal exposure to per- and polyfluoroalkyl substances and infant growth and adiposity: The healthy start study	2019	Environ Int. 2019 Oct;131:104983. doi: 10.1016/j.envint.2019.104983. Epub 2019 Jul 5.	BACKGROUND: Prenatal exposures to certain per- and polyfluoroalkyl substances (PFAS) have been linked to lower weight and adiposity at birth but greater weight and adiposity in childhood. We hypothesized that faster growth in early infancy may be associated with maternal PFAS concentrations.METHODS: Among 415 mother-infant pairs in a longitudinal cohort study, we estimated associations between maternal pregnancy serum concentrations of six PFAS and offspring weight and adiposity at ~5 months of age, and growth in early infancy. Linear and logistic regression models were adjusted for potential confounders including maternal pre-pregnancy body mass index. Effect modification by infant sex was evaluated. We evaluated potential confounding by correlated exposures via multipollutant linear regression and elastic net penalized regression.RESULTS: Associations between maternal PFAS concentrations and infant weight and adiposity differed by offspring sex. In male infants, maternal perfluorooctanoate and perfluorononanoate were positively associated with adiposity, with percent fat mass increases of 1.5-1.7% per ln-ng/mL increase in PFAS (median adiposity at ~5 months: 24.6%). Maternal perfluorooctane sulfonate (PFOS) and perfluorohexane sulfonate (PFHxS) were associated with lower weight-for-age z-score among female infants only (-0.26 SD per ln-ng/mL PFOS, 0.95 CI -0.43, -0.10; -0.17 SD per ln-ng/mL PFHxS, 0.95 CI -0.33, -0.01). In analyses pooled by sex, 2-(N-methyl-perfluorooctane sulfonamido) acetate above vs. below the limit of detection was associated with greater odds of rapid growth in weight-for-age (odds ratio [OR] 2.2, 0.95 CI 1.1, 4.3) and weight-for-length (OR 3.3, 0.95 CI 1.8, 6.2). Multipollutant models generally confirmed the results and strengthened some associations.DISCUSSION: We observed sex- and chemical-specific associations between maternal serum PFAS concentrations and infant weight and adiposity. Multipollutant models suggested confounding by correlated PFAS with opposing effects. Although maternal PFAS concentrations are inversely associated with infant weight and adiposity at birth, rapid gain may occur in infancy, particularly in fat mass.	●	●								-	1	A	-
598	ヒト（生殖毒性）	Starling, A. P.; Adgate, J. L.; Hamman, R. F.; Kechris, K.; Calafat, A. M.; Ye, X.; Dabelea, D.	Perfluoroalkyl substances during pregnancy and offspring weight and adiposity at birth: Examining mediation by maternal fasting glucose in the healthy start study	2017	Environ Health Perspect. 2017 Jun 26;125(6):067016. doi: 10.1289/EHP641.	BACKGROUND: Certain perfluoroalkyl and polyfluoroalkyl substances (PFAS) are widespread, persistent environmental contaminants. Prenatal PFAS exposure has been associated with lower birth weight; however, impacts on body composition and factors responsible for this association are unknown.OBJECTIVES: We aimed to estimate associations between maternal PFAS concentrations and offspring weight and adiposity at birth, and secondarily to estimate associations between PFAS concentrations and maternal glucose and lipids, and to evaluate the potential for these nutrients to mediate associations between PFAS and neonatal outcomes.METHODS: Within the Healthy Start prospective cohort, concentrations of 11 PFAS, fasting glucose, and lipids were measured in maternal mid-pregnancy serum (). Infant body composition was measured using air displacement plethysmography. Associations between PFAS and birth weight and adiposity, and between PFAS and maternal glucose and lipids, were estimated via linear regression. Associations were decomposed into direct and indirect effects.RESULTS: Five PFAS were detectable in of participants. Maternal perfluorooctanoate (PFOA) and perfluorononanoate (PFNA) concentrations were inversely associated with birth weight. Adiposity at birth was approximately 0.1 lower in the highest categories of PFOA, PFNA, and perfluorohexane sulfonate (PFHxS) compared to the lowest categories. PFOA, PFNA, perfluorodecanoate (PFDeA), and PFHxS were inversely associated with maternal glucose. Up to 0.116 of the effect of PFAS on neonatal adiposity was mediated by maternal glucose concentrations. Perfluorooctane sulfonate (PFOS) was not significantly associated with any outcomes studied.CONCLUSIONS: Follow-up of offspring will determine the potential long-term consequences of lower weight and adiposity at birth associated with prenatal PFAS exposure.	●	●		●						-	1	A	-
599	ヒト（生殖毒性）	Starling, A. P.; Engel, S. M.; Richardson, D. B.; Baird, D. D.; Haug, L. S.; Stuebe, A. M.; Klungsoyr, K.; Harmon, Q.; Becher, G.; Thomsen, C.; Sabaredzovic, A.; Eggesbo, M.; Hoppin, J. A.; Travlos, G. S.; Wilson, R. E.; Trogstad, L. I.; Magnus, P.,er; Longnecker, M. P.	Perfluoroalkyl Substances During Pregnancy and Validated Preeclampsia Among Nulliparous Women in the Norwegian Mother and Child Cohort Study	2014	Am J Epidemiol. 2014 Apr 1;179(7):824-33. doi: 10.1093/aje/kwt432. Epub 2014 Feb 20.	Perfluoroalkyl substances (PFAS) are persistent and ubiquitous environmental contaminants, and human exposure to these substances may be related to preeclampsia, a common pregnancy complication. Previous studies have found serum concentrations of PFAS to be positively associated with pregnancy-induced hypertension and preeclampsia in a population with high levels of exposure to perfluorooctanoate. Whether this association exists among pregnant women with background levels of PFAS exposure is unknown. Using data from the Norwegian Mother and Child Cohort Study conducted by the Norwegian Institute of Public Health, we carried out a study of nulliparous pregnant women enrolled in 20032007 (466 cases, 510 noncases) to estimate associations between PFAS concentrations and an independently validated diagnosis of preeclampsia. We measured levels of 9 PFAS in maternal plasma extracted midpregnancy; statistical analyses were restricted to 7 PFAS that were quantifiable in more than 50 of samples. In proportional hazards models adjusted for maternal age, prepregnancy body mass index (weight (kg)/height (m)(2)), educational level, and smoking status, we observed no strongly positive associations between PFAS levels and preeclampsia. We found an inverse association between preeclampsia and the highest quartile of perfluoroundecanoic acid concentration relative to the lowest quartile (hazard ratio 0.55, 95 confidence interval: 0.38, 0.81). Overall, our findings do not support an increased risk of preeclampsia among nulliparous Norwegian women with background levels of PFAS exposure.	●	●		●						-		B	-
600	ヒト（発生毒性）	Steenland, K.; Kugathasan, S.; Barr, D. B.	PFOA and ulcerative colitis	2018	Environ Res. 2018 Aug;165:317-321. doi: 10.1016/j.envres.2018.05.007. Epub 2018 May 16.	INTRODUCTION: PFOA (perfluoroctanoic acid) is a perfluoroalkyl substance (PFAS). Although use in the US has been phased out, PFOA persists indefinitely in the environment, and is present in the serum of virtually all people in industrialized countries. Approximately 6 million Americans drink water comtaminated with PFOA above EPA-recommended levels. In a previous cohort study (n = 32,000), we found a strong positive exposure-response relation between PFOA serum levels and subsequent ulcerative colitis (UC) in a high-exposed population from the mid-Ohio valley, but no association with Crohn's disease. In the present study we aimed to determine if UC cases had higher levels of PFOA than did controls or Crohn's disease patients.METHODS: We measured PFOA and three other PFAS in the serum of 114 UC patients, 60 Crohn's disease patients, and 75 controls, within a year of diagnosis. We conducted regression analyses to assess the association of the PFAS with diagnosis.RESULTS: The mean age of subjects was 17 years. The mean year of diagnosis was 2007 Mean levels of PFAS were similar to US levels. Mean log PFOA level in UC patients was 0.38 higher (p = 0.01) than the combined group of Crohn's disease and controls. In contrast, the three other PFASs were significantly higher in controls and Crohn's patients than UC patients. The odds ratio for UC per one unit of log PFOA was 1.6 (95% CI 1.14-2.24), but the trend by quintiles was not monotonic (1, 0.84, 40.98, 33.36, 2.86).CONCLUSION: We found higher serum PFOA in UC cases compared to Crohn's disease patients or controls, in contrast to other PFAS. Our research is limited by not knowing if the elevated PFOA preceded UC in this population.	●	●								-		C	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
601	ヒト（発生毒性）	Stein, C. R.; Savitz, D. A.; Bellinger, D. C.	Perfluorooctanoate and neuropsychological outcomes in children	2013	Epidemiology. 2013 Jul;24(4):590-9. doi: 10.1097/EDE.0b013e3182944432.	BACKGROUND: In animal studies, perfluorinated compounds affect fetal growth, development, viability, and postnatal growth. The limited epidemiologic findings on child neurobehavioral development are mixed.METHODS: We recruited and evaluated 320 children who participated in the C8 Health Project, a 2005-2006 survey in a Mid-Ohio Valley community highly exposed to perfluorooctanoate (PFOA) through contaminated drinking water. We examined associations among estimated in utero PFOA exposure, measured childhood PFOA serum concentration, and subsequent performance on neuropsychological tests 3-4 years later at ages 6-12 years. We assessed Intelligence Quotient (IQ) reading and math skills, language, memory and learning, visual-spatial processing, and attention. All multivariable linear regression models were adjusted for age, sex, home environment, test examiner, and maternal IQ. Models with measured childhood PFOA were additionally adjusted for child body mass index.RESULTS: Children in the highest as compared with lowest quartile of estimated in utero PFOA had increases in Full Scale IQ (β 4.6, 0.95 confidence interval [CI] = 0.7-8.5) and decreases in characteristics of attention deficit/hyperactivity disorder as measured by the Clinical Confidence Index of Connors' Continuous Performance Test-II (β -8.5, 0.95 CI = -16.1 to -0.8). There were negligible associations between PFOA and reading or math skills or neuropsychological functioning.CONCLUSION: These results do not suggest an adverse association between the levels of PFOA exposure experienced by children in this cohort and their performance on neuropsychological tests.	●	●		●						-		B	-
602	ヒト（発生毒性）	Stein, Cheryl R; Savitz, David A; Bellinger, David C	Perfluorooctanoate exposure in a highly exposed community and parent and teacher reports of behaviour in 6-12-year-old children	2014	Paediatr Perinat Epidemiol. 2014 Mar;28(2):146-56. doi: 10.1111/ppe.12097. Epub 2013 Dec 9.	BACKGROUND: In toxicology studies, perfluorinated compounds affect fetal growth, development, viability, and postnatal growth. There are limited epidemiologic studies on child development. METHODS: We recruited and evaluated 321 children who participated in the C8 Health Project, a 2005-06 survey in a mid-Ohio Valley community highly exposed to perfluorooctanoate (PFOA) through contaminated drinking water. We examined associations between measured childhood PFOA serum concentration and mother and teacher reports of executive function (Behaviour Rating Inventory of Executive Function), attention deficit hyperactivity disorder (ADHD)-like behaviour (Conner's ADHD Diagnostic and Statistical Manual of Mental Disorders IV Scales), and behavioural problems (Behaviour Assessment System for Children) assessed 3 to 4 years later at ages 6-12 years. RESULTS: Overall, neither reports from mothers nor teachers provided clear associations between exposure and child behaviour. Mother reports, however, did suggest favourable associations between exposure and behaviour among boys and adverse associations among girls. On the composite scale from the Behaviour Rating Inventory of Executive Function (n = 318), PFOA exposure had a favourable association among boys (highest vs. lowest quartile β = -6.39; 95% confidence interval [CI] -11.43, -1.35) and an adverse association among girls (highest vs. lowest quartile β = 4.42; 95% CI -0.03, 8.87; interaction P = 0.01). Teacher reports (n = 189) replicated some, but not all of the sex interactions observed in mothers' reports. CONCLUSIONS: Aggregate results did not suggest adverse effects of PFOA on behaviour, but sex-specific results raise the possibility of differing patterns by sex. Results are not consistent between mothers' and teachers' reports. Effect modification by sex may warrant further investigation.	●	●		●						-		B	-
603	ヒト（発生毒性）	Stein, C. R.; Savitz, D. A.; Dougan, M.	Serum levels of perfluorooctanoic acid and perfluorooctane sulfonate and pregnancy outcome	2009	Am J Epidemiol. 2009 Oct 1;170(7):837-46. doi: 10.1093/aje/kwp212. Epub 2009 Aug 19.	The authors examined the association of serum perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) with self-reported pregnancy outcome in Mid-Ohio Valley residents (2000-2006) highly exposed to PFOA. Data on 1845 pregnancies within the 5 years preceding exposure measurement were analyzed for PFOA, and data on 5262 pregnancies were analyzed for PFOS. Generalized estimating equations were used to calculate adjusted odds ratios and 0.95 confidence intervals. Neither PFOA nor PFOS showed any association with miscarriage or preterm birth. Preeclampsia was weakly associated with PFOA (adjusted odds ratio = 1.3, 0.95 confidence interval: 0.9, 1.9) and PFOS (adjusted odds ratio = 1.3, 0.95 confidence interval: 1.1, 1.7) exposures above the median. PFOA was not associated with an increase in low birth weight, but PFOS showed an increased risk above the median (adjusted odds ratio = 1.5, 0.95 confidence interval: 1.1, 1.9) and a dose-response gradient. Birth defects were weakly associated with PFOA exposures above the 90th percentile (adjusted odds ratio = 1.7, 0.95 confidence interval: 0.8, 3.6). This study identified modest associations of PFOA with preeclampsia and birth defects and of PFOS with preeclampsia and low birth weight, but associations were small, limited in precision, and based solely on self-reported health outcomes.	●	●		●	●	●	●			-		C	-
604	ヒト（発生毒性）	Stein, Cheryl R; Wolff, Mary S; Calafat, Antonia M; Kato, Kayoko; Engel, Stephanie M	Comparison of polyfluoroalkyl compound concentrations in maternal serum and amniotic fluid: a pilot study	2012	Reprod Toxicol. 2012 Nov;34(3):312-6. doi: 10.1016/j.reprotox.2012.05.039. Epub 2012 May 18.	The extent to which polyfluoroalkyl compounds (PFCs) are detectable in amniotic fluid is unknown. Using paired samples from 28 women, we compared the concentration of 8 PFCs measured in serum, the standard matrix for assessing human exposure, amniotic fluid from routine amniocentesis, and urine. Perfluorooctanoate (PFOA), perfluorononanoate (PFNA), perfluorooctane sulfonate (PFOS), and perfluorohexane sulfonate (PFHxS) were detected in all maternal serum samples. The number of amniotic fluid samples with detectable concentrations differed by PFC (PFOA n=24; PFNA n=10; PFOS n=9; PFHxS n=4). The correlation coefficient between maternal serum and amniotic PFC levels varied considerably by PFC (PFOA ρ=0.64, p<0.001; PFNA ρ=0.05, p=0.9; PFOS ρ=0.76, p=0.01; PFHxS ρ=0.80, p=0.2). Using linear regression, PFOA appeared to be commonly detected in amniotic fluid if the serum concentration exceeded approximately 1.5 ng/mL whereas PFOS was rarely detected in amniotic fluid until the serum concentration was about 5.5 ng/mL. No PFCs were detected in urine.	●	●								-		B	-
605	ヒト（発生毒性）	Strøm, M.; Hansen, S.; Olsen, S. F.; Haug, L. S.; Rantakokko, P.; Kiviranta, H.; Halldorsson, T. I.	Persistent organic pollutants measured in maternal serum and offspring neurodevelopmental outcomes--a prospective study with long-term follow-up	2014	Environ Int. 2014 Jul;68:41-8. doi: 10.1016/j.envint.2014.03.002. Epub 2014 Apr 2.	Fetal exposure to persistent organic pollutants (POPs) has been linked to adverse neurodevelopment, but few studies have had follow-up beyond childhood. The purpose of this study was to examine the association of maternal serum concentrations of two perfluoroalkyl acids (perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS)), polychlorinated biphenyls (PCBs), dichlorodiphenyldichloroethylene (p,p'-DDE) and hexachlorobenzene (HCB) with offspring behavioural and affective disorders and scholastic achievement in a prebirth cohort study with 20 years of follow up. Between 1988 and 1989 pregnant women (n=965) were recruited for the prebirth Danish Fetal Origins 1988 (DaFO88) Cohort in Aarhus, Denmark. Perfluoroalkyl acids, PCBs, p,p'-DDE, and HCB were quantified in serum from week 30 of gestation (n=876 for perfluoroalkyl acids/872 for PCBs, p,p'-DDE, HCB). Offspring were followed up through national registries until 2011 We evaluated associations between maternal serum concentrations of these POPs and offspring neurodevelopmental outcomes, defined as: first admission diagnosis or prescription of medication until age >20 for -1 ADHD; -2 depression; and -3 scholastic achievement defined as mean grade on a standardized written examination given in the 9th grade (final exams of compulsory school in Denmark). Maternal concentrations of organochlorine substances and perfluoroalkyl acids were higher than present day levels. During the follow-up period there were 27 -0.031 cases of ADHD and 104 -0.119 cases of depression; the mean scholastic achievement was 6.7 (SD 2.3). Overall we found no association for maternal levels of any of the measured pollutants with offspring behavioural and affective disorders or with scholastic achievement. Our analyses based on biomarkers from a cohort of over 800 pregnant women with long-term close to complete follow-up through national registries showed little evidence of a programming effect of PFOA, PFOS, PCBs, p,p'-DDE, and HCB in relation to clinically and functionally relevant offspring neurodevelopmental outcomes.	●	●		●						-		B	-
606	ヒト（発生毒性）	Tanner, E. M.; Bornehag, C. G.; Gennings, C.	Dynamic growth metrics for examining prenatal exposure impacts on child growth trajectories: Application to perfluorooctanoic acid (PFOA) and postnatal weight gain	2020	Environ Res. 2020 Mar;182:109044. doi: 10.1016/j.envres.2019.109044. Epub 2019 Dec 14.	BACKGROUND: Epidemiologic studies investigating prenatal exposures in relation to growth typically rely on cumulative growth measures such as weight or BMI. However, less is known about how prenatal exposure may impact other aspects of growth dynamics, including timing and velocity.OBJECTIVES: To describe and apply a nonlinear growth model previously used in other health science fields to characterize postnatal growth trajectories for use in environmental epidemiology studies.METHODS: We used a double logistic function to model child weight trajectories from birth to 5.5 years using data from the Swedish Environmental Longitudinal Mother and Child, Asthma and Allergy (SELMA) study. From this, we approximated several infant growth metrics: 1) duration of time needed to complete 0.9 of the infant growth spurt (Δt1), 2) the maximum growth rate in infancy or infant peak growth velocity (PGV), 3) the age at infant PGV (δ1), a measure of growth tempo, and 4) the weight plateau at the end of the infant growth spurt (α1). We assessed these metrics in relation to prenatal perfluorooctanoic acid (PFOA) exposure among 1334 mother-child pairs, and differences between boys and girls.RESULTS: Average estimated infant PGV and its timing (δ1) were 0.68 kg/month and 3.4 months, respectively. Mean infant growth spurt duration (Δt1) was 13 months, ending at an average weight plateau (α1) of 8.2 kg. Higher prenatal PFOA concentrations were related to a longer duration of infant growth (Δt1: 0.06; 0.95 CI = 0.01, 0.11). PGV was not impacted, but higher prenatal PFOA concentrations were significantly related to delayed infant PGV (δ1: 0.58; 0.95 CI = 0.17, 0.99) and a higher post-spurt weight plateau (α1: 0.81; 0.95 CI = 0.21, 1.41). After adjusting for FALSE discovery, results were only significant for δ1 and α1. We observed a significant interaction by sex for the association with δ1, and stratified analyses revealed the association was only significant among girls.CONCLUSION: Model-derived growth metrics were consistent with published growth standards. This novel application of nonlinear growth modeling enabled detection of altered infant growth dynamics in relation to prenatal PFOA exposure. Our results may help describe how PFOA yields lower birthweights, but higher weight later in childhood. Future applications may characterize adolescent growth or additional metrics of biological interest.	●	●								-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①抽出	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
607	ヒト（発達神経毒性）	Tanner, E. M.; Hallerbäck, M. U.; Wikström, S.; Lindh, C.; Kiviranta, H.; Gennings, C.; Bornehag, C. G.	Early prenatal exposure to suspected endocrine disruptor mixtures is associated with lower IQ at age seven	2020	Environ Int. 2020 Jan;134:105185. doi: 10.1016/j.envint.2019.105185. Epub 2019 Oct 24.	Background: Endocrine disrupting chemicals (EDCs) are xenobiotics with the ability to interfere with hormone action, even at low levels. Prior environmental epidemiology studies link numerous suspected EDCs, including phthalates and bisphenol A (BPA), to adverse neurodevelopmental outcomes. However, results for some chemicals were inconsistent and most assessed one chemical at a time. Objectives: To evaluate the overall impact of prenatal exposure to an EDC mixture on neurodevelopment in school-aged children, and identify chemicals of concern while accounting for co-exposures. Methods: Among 718 mother-child pairs from the Swedish Environmental Longitudinal, Mother and child, Asthma and allergy study (SELMA) study, we used Weighted Quantile Sum (WQS) regression to assess the association between 26 EDCs measured in 1st trimester urine or blood, with Wechsler Intelligence Scale for Children (IV) Intelligence Quotient (IQ) scores at age 7 years. Models were adjusted for child sex, gestational age, mother's education, mother's IQ (RAVEN), weight, and smoking status. To evaluate generalizability, we conducted repeated holdout validation, a machine learning technique. Results: Using repeated holdout validation, IQ scores were 1.9-points (CI = -3.6, -0.2) lower among boys for an inter-quartile-range (IQR) change in the WQS index. BPF made the largest contribution to the index with a weight of 14%. Other chemicals of concern and their weights included PBA (9%), TCP (9%), MEP (6%), MBzP (4%), PFOA (6%), PFOS (5%), PFHxS (4%), Triclosan (5%), and BPA (4%). While we did observe an inverse association between EDCs and IQ among all children when training and testing the WQS index estimate on the full dataset, these results were not robust to repeated holdout validation. Conclusion: Among boys, early prenatal exposure to EDCs was associated with lower intellectual functioning at age 7. We identified bisphenol F as the primary chemical of concern, suggesting that the BPA replacement compound may not be any safer for children. Future studies are needed to confirm the potential neurotoxicity of replacement analogues.	●	●							-	1	A	-
608	ヒト（発生毒性）	Thorsdottir, I.; Birgisdottir, B. E.	Different weight gain in women of normal weight before pregnancy: postpartum weight and birth weight	1998	Obstet Gynecol. 1998 Sep;92(3):377-83. doi: 10.1016/s0029-7844(98)00187-2.	OBJECTIVE: To identify the effect of different gestational weight gains among women of normal weight before pregnancy on babies' birth weights, and women's weights 18-24 months postpartum.METHODS: Two groups of women of normal weight before pregnancy (body mass index [BMI] 19.6-25.4 kg/m2) took part in the study (n = 200). They gained either moderate weight (9-15 kg) or high weight (18-24 kg) during pregnancy. From maternity records and telephone interviews, information on age, height, prepregnancy and postpartum weight, gestational weight gain, babies' birth weights, lactation, parity, and smoking habits was collected.RESULTS: High maternal weight gain during pregnancy resulted in mean birth weight 286 g higher than that of babies of mothers who gained moderate weight. The correlation coefficient between birth weight and gestational weight gain was 0.3 (P < .001). The postpartum weight of women with high weight gain during pregnancy was 2.6+/-0.38 kg (mean +/- standard error of the mean [SEM]) more than before pregnancy but the group of moderate weight gain weighed 0.1+/-0.47 kg less than before pregnancy (P < .001). However, most women in both groups -0.886 regained normal weight, and prepregnant weight correlated strongly with the weight 18-24 months postpartum (r =0.79, P < .001). There was not a significant correlation between the duration of lactation and postpartum weight loss (r = 0.04, P > .05).CONCLUSION: High gestational weight gain among women of normal weight before pregnancy increases birth weight and women's weight postpartum, compared with moderate weight gain. Prepregnant weight is more indicative of postpartum weight, and women reach normal weight again irrespective of gestational weight gain.	●	●							-		D	-
609	ヒト（発生毒性）	Tian, Mei; Reichetzeder, Christoph; Li, Jian; Hocher, Berthold	Low birth weight, a risk factor for diseases in later life, is a surrogate of insulin resistance at birth	2019	J Hypertens. 2019 Nov;37(11):2123-2134. doi: 10.1097/HJH.0000000000002156.	: Low birth weight (LBW) is associated with diseases in adulthood. The birthweight attributed risk is independent of confounding such as gestational age, sex of the newborn but also social factors. The birthweight attributed risk for diseases in later life holds for the whole spectrum of birthweight. This raises the question what pathophysiological principle is actually behind the association. In this review, we provide evidence that LBW is a surrogate of insulin resistance. Insulin resistance has been identified as a key factor leading to type 2 diabetes, cardiovascular disease as well as kidney diseases. We first provide evidence linking LBW to insulin resistance during intrauterine life. This might be caused by both genetic (genetic variations of genes controlling glucose homeostasis) and/or environmental factors (due to alterations of macronutrition and micronutrition of the mother during pregnancy, but also effects of paternal nutrition prior to conception) leading via epigenetic modifications to early life insulin resistance and alterations of intrauterine growth, as insulin is a growth factor in early life. LBW is rather a surrogate of insulin resistance in early life - either due to inborn genetic or environmental reasons - rather than a player on its own.	●	●							-		D	-
610	ヒト（生殖毒性）	Tian, Y.; Liang, H.; Miao, M.; Yang, F.; Ji, H.; Cao, W.; Liu, X.; Zhang, X.; Chen, A.; Xiao, H.; Hu, H.; Yuan, W.	Maternal plasma concentrations of perfluoroalkyl and polyfluoroalkyl substances during pregnancy and anogenital distance in male infants	2019	Hum Reprod. 2019 Jul 8;34(7):1356-1368. doi: 10.1093/humrep/dez058.	STUDY QUESTION: Are maternal plasma concentrations of perfluoroalkyl and polyfluoroalkyl substances (PFASs) during pregnancy associated with anogenital distance (AGD) in male infants at birth, 6, and 12 months of age?SUMMARY ANSWER: Higher maternal plasma concentrations of some PFASs were associated with shorter AGD in male infants at birth and 6 months of age.WHAT IS KNOWN ALREADY: Two animal studies have found that exposure to PFASs was associated with shorter AGD in male rat fetuses and wild male minks. There is only one human study on the topic that did not identify consistent patterns between maternal serum concentrations of PFASs during pregnancy and AGD in male infants.STUDY DESIGN, SIZE, DURATION: In the prospective cohort study, a total of 1292 eligible pregnant women were recruited at 12-16 weeks of gestation between April and December 2012 at the Maternal and Child Health Hospital of Minhang district in Shanghai, China. At delivery, 667 male singletons were born. They were then followed up at birth (n = 439) and at 6 (n = 411) and 12 months (n = 376) of age when anopenile distance (AGDAP) and anoscrotal distance (AGDAS) were measured.PARTICIPANTS/MATERIALS, SETTING, METHODS: A total of 500 male infants who had both maternal plasma concentrations of PFASs and at least one AGD measurement of at three time points were included in the present study. Multiple linear regression models were used to evaluate the potential linear associations between maternal concentrations of PFASs and AGD.MAIN RESULTS AND THE ROLE OF CHANCE: Maternal plasma concentrations (ln-transformed) of perfluorooctane sulfonate (PFOS), perfluorodecanoic acid (PFDA), and perfluoroundecanoic acid (PFUdA) were inversely associated with AGDAS or AGDAP at birth (AGDAS: per ln unit increase in PFAS concentrations: β (95% CI): -0.65 (-1.27 to -0.02) mm for PFOS; -0.58 (-1.11 to -0.06) mm for PFDA; and -0.57 (-1.09 to -0.06) mm for PFUdA; AGDAP: per ln unit increase in PFAS concentrations: β (95% CI): -0.63 (-1.24 to -0.01) mm for PFDA and - 0.76 (-1.36 to -0.16) mm for PFUdA). At 6 months of age, per unit increase in maternal ln concentrations of PFOS and perfluorotridecanoic acid (PFTrDA), AGDAS decreased on average by -2.21 (95% CI: -4.28 to -0.14) and -1.11 (95% CI: -2.17 to -0.06) mm, respectively. Additionally, ln-transformed perfluorooctanoic acid (PFOA) showed nonsignificant but inverse associations with both AGDAS and AGDAP at 6 months of age. We found no significant associations between ln-transformed maternal concentrations of PFASs and either AGDAS or AGDAP at 12 months of age. However, significantly	●	●							-		B	-
611	ヒト（発生毒性）	Toft, G.; Jönsson, B. A.; Bonde, J. P.; Nørgaard-Pedersen, B.; Hougaard, D. M.; Cohen, A.; Lindh, C. H.; Ivell, R.; Anand-Ivell, R.; Lindhard, M. S.	Perfluorooctane Sulfonate Concentrations in Amniotic Fluid, Biomarkers of Fetal Leydig Cell Function, and Cryptorchidism and Hypospadias in Danish Boys (1980-1996)	2016	Environ Health Perspect. 2016 Jan;124(1):151-6. doi: 10.1289/ehp.1409288. Epub 2015 Jun 5.	BACKGROUND: Exposure to perfluorooctane sulfonate (PFOS) may potentially disturb fetal Leydig cell hormone production and male genital development.OBJECTIVES: We aimed to study the associations between levels of amniotic fluid PFOS, fetal steroid hormone, and insulin-like factor 3 (INSL3) and the prevalence of cryptorchidism and hypospadias.METHODS: Using the Danish National Patient Registry, we selected 270 cryptorchidism cases, 75 hypospadias cases, and 300 controls with stored maternal amniotic fluid samples available in a Danish pregnancy-screening biobank (1980-1996). We used mass spectrometry to measure PFOS in amniotic fluid from 645 persons and steroid hormones in samples from 545 persons. INSL3 was measured by immunoassay from 475 persons. Associations between PFOS concentration in amniotic fluid, hormone levels, and genital malformations were assessed by confounder-adjusted linear and logistic regression.RESULTS: The highest tertile of PFOS exposure (> 1.4 ng/mL) in amniotic fluid was associated with a 0.4 (95% CI: -69, -11%) lower INSL3 level and an 0.18 (95% CI: 7, 29%) higher testosterone level compared with the lowest tertile (< 0.8 ng/mL). Amniotic fluid PFOS concentration was not associated with cryptorchidism or hypospadias.CONCLUSIONS: Environmental PFOS exposure was associated with steroid hormone and INSL3 concentrations in amniotic fluid, but was not associated with cryptorchidism or hypospadias in our study population. Additional studies are needed to determine whether associations with fetal hormone levels may have long-term implications for reproductive health.CITATION: Toft G, Jönsson BA, Bonde JP, Nørgaard-Pedersen B, Hougaard DM, Cohen A, Lindh CH, Ivell R, Anand-Ivell R, Lindhard MS. 2016 Perfluorooctane sulfonate concentrations in amniotic fluid, biomarkers of fetal Leydig cell function, and cryptorchidism and hypospadias in Danish boys (1980-1996).	●	●		●					-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献①ラン	文献②ラン
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
612	ヒト（生殖毒性）	Tsai, M. S.; Lin, C. Y.; Lin, C. C.; Chen, M. H.; Hsu, S. H.; Chien, K. L.; Sung, F. C.; Chen, P. C.; Su, T. C.	Association between perfluoroalkyl substances and reproductive hormones in adolescents and young adults	2015	Int J Hyg Environ Health. 2015 Jul;218(5):437-43. doi: 10.1016/j.ijheh.2015.03.008.	BACKGROUND: Few studies have explored the association between perfluoroalkyl substances (PFAS) and reproductive hormones in adolescents and young adults.OBJECTIVES: This study aimed to investigate the association of PFAS with reproductive hormones in adolescents and young adults.METHODS: We recruited 540 subjects aged 44925 years from a 1992 to 2000 mass urine screening population and established a cohort from 2006 to 2008 via invitations by mail or/and telephone. Serum PFAS levels were analyzed with a Waters ACQUITY UPLC system coupled with a Waters Quattro Premier XE triple quadrupole mass spectrometer. Serum reproductive hormone levels were measured by immunoluminometric assay with an Architect random access assay system. PFAS levels were divided into different percentiles according to their detection limits in the multiple regression models to analyze associations between reproductive hormone levels and exposure with PFAS.RESULTS: The adjusted mean serum level of sex hormone-binding globulin (SHBG) decreased significantly in association with the <50th, 50-75, 75-90 and >90th percentile categories of perfluorooctanoic acid (PFOA) compared with a reference category for the females in the 12-17-year-old group. The follicle-stimulating hormone (FSH) levels were significantly decreased in association with the different percentile categories of perfluorooctane sulfonate (PFOS) in the male 12-17-year-old group and the different percentile categories of perfluoroundecanoic acid (PFUA) in the female 12-17-year-old group. The serum FSH levels in the females aged 44912 were also decreased in association with the different percentile categories of PFUA. On the other hand, there was a significantly negative association between the different percentile categories of PFOS and the serum testosterone level among the female 12-17-year-old group.CONCLUSIONS: We found that the serum concentrations of PFOA, PFOS, and PFUA were negatively associated with the serum levels of SHBG, FSH, and testosterone in the young Taiwanese population and that these effects were the strongest in the females aged 12-17. Further studies are needed to determine whether these associations are causal.	●	●		●					●	-		B	-
613	ヒト（生殖毒性）	U.S. EPA,	Drinking water health advisory for perfluorooctanoic acid (PFOA) [EPA Report]	2016	EPA 822-R-16-005. Washington, DC: U.S. Environmental Protection Agency, Office of Water.	Perfluorooctanoic acid (PFOA) is a synthetic, fully fluorinated organic acid; it used in a variety of consumer products and in the production of fluoropolymers, and it is generated as a degradation product of other perfluorinated compounds. Because of strong carbon-fluorine bonds, PFOA is stable to metabolic and environmental degradation. PFOA is one of a large group of perfluoroalkyl substances (PFASs) that are used to make products more resistant to stains, grease, and water. These compounds have been widely found in consumer and industrial products, as well as in food items. Major U.S. manufacturers voluntarily agreed to phase out production of PFOA by the end of 2015 Exposure to PFOA in the United States remains possible due to its legacy uses, existing and legacy uses on imported goods, degradation of precursors, and extremely high persistence in the environment and the human body. PFOA was detected in blood serum in 0.99 of the U.S. general population between 1999 and 2012; however, the levels of PFOA in blood have been decreasing since U.S. companies began to phase out production. Water resources contaminated by PFOA have been associated with releases from manufacturing sites, industrial sites, fire/crash training areas, and industrial or municipal waste sites where products are disposed of or applied. The U.S. Environmental Protection Agency (EPA) is issuing a lifetime drinking water Health Advisory (HA) for PFOA of 0.07 micrograms per liter (µg/L) based on a reference dose (RfD) derived from a developmental toxicity study in mice; the critical effects included reduced ossification in proximal phalanges and accelerated puberty in male pups following exposure during gestation and lactation. PFOA is known to be transmitted to the fetus in cord blood and to the newborn in breast milk. This lifetime HA is based on the latest health effects information for noncancer and cancer effects for PFOA as described in EPA's 2016 Health Effects Support Document for Perfluorooctanoic Acid (PFOA), which was revised following external peer review. Because the developing fetus and newborn are particularly sensitive to PFOA-induced toxicity, the RfD based on developmental effects also is protective of adverse effects in adults (e.g., liver and kidney toxicity). The lifetime HA is therefore protective of the population at large. For PFOA, oral animal studies of short-term, subchronic, and chronic duration are available in multiple species including monkeys, rats and mice. These studies report developmental effects (survival, body weight changes, reduced ossification, delays in eye opening,	●									評価書		D	-
614	ヒト（生殖毒性）	Vagi, S. J.; Azziz-Baumgartner, E.; Sjödin, A.; Calafat, A. M.; Dumesic, D.; Gonzalez, L.; Kato, K.; Silva, M. J.; Ye, X.; Azziz, R.	Exploring the potential association between brominated diphenyl ethers, polychlorinated biphenyls, organochlorine pesticides, perfluorinated compounds, phthalates, and bisphenol a in polycystic ovary syndrome: a case-control study	2014	BMC Endocr Disord. 2014 Oct 28;14:86. doi: 10.1186/1472-6823-14-86.	BACKGROUND: Polycystic Ovary Syndrome (PCOS) is an endocrine-metabolic disorder that affects approximately 6-10% of women of child-bearing age. Although preliminary studies suggest that certain pollutants may act as endocrine disruptors in animals, little is known about their potential association with PCOS. The objective of this case-control pilot study is to determine whether women with PCOS have higher concentrations of specific environmental contaminants compared to women who have not developed PCOS.METHODS: Fifty-two PCOS case-patients (diagnosed using the National Institutes of Health 1990 definition) and 50 controls were recruited in 2007-2008, from an urban academic medical center in Los Angeles, CA. Brominated diphenyl ethers, polychlorinated biphenyls (PCBs), organochlorine pesticides, and perfluorinated compounds (PFCs) were measured in serum, and phthalates metabolites and bisphenol A (BPA) in urine.RESULTS: PCOS case-patients had significantly higher geometric mean (GM) serum concentrations of two PFCs: perfluorooctanoate (PFOA) (GMcases = 4.1 µg/L, GMcontrols = 2.3 µg/L; p = 0.001) and perfluorooctane sulfonate (PFOS) (GMcases = 8.2 µg/L, GMcontrols = 4.9 µg/L; p = 0.01), and lower urinary concentrations of monobenzyl phthalate (mBzP) (GMcases = 7.5 µg/g creatinine, GMcontrols = 11.7 µg/g creatinine; p = 0.02). Logistic regression, controlling for body mass index, age and race, identified an increased likelihood of PCOS in subjects with higher serum concentrations of PFOA and PFOS (adjusted-ORs = 5.8-6.9, p < 0.05), and with lower urine concentrations of mBzP and mono-n-butyl phthalate (mBP) (aORs = 0.14-0.25, p < 0.05).CONCLUSIONS: Our data suggest that PCOS case-patients may differ from controls in their environmental contaminant profile. PCOS subjects had higher serum concentrations of two PFCs, PFOA and PFOS, and lower urine concentrations of mBP and mBzP. Future studies are needed to confirm these preliminary findings and determine if these chemicals or their precursors may have a role in the pathogenesis of PCOS.	●	●		●						-		C	-
615	ヒト（発生毒性）	Valvi, D.; Oulhote, Y.; Weihe, P.; Dalgård, C.; Bjerve, K. S.; Steuerwald, U.; Grandjean, P.	Gestational diabetes and offspring birth size at elevated environmental pollutant exposures	2017	Environ Int. 2017 Oct;107:205-215. doi: 10.1016/j.envint.2017.07.016. Epub 2017 Jul 25.	BACKGROUND: Gestational diabetes mellitus (GDM) is associated with increased availability of glucose and macronutrients in fetal circulation and macrosomia. Therefore, the role of GDM in the association between metabolism-disrupting chemicals and birth size deserves attention.OBJECTIVE: We examined whether GDM may mediate or modify the associations between maternal environmental pollutant exposures and offspring birth size measures.METHODS: We analyzed 604 Faroese pregnant women and their offsprings born in 1997-2000. Maternal pregnancy serum concentrations of organochlorine compounds (OCs: polychlorinated biphenyl (PCB) congeners and dichlorodiphenyldichloroethylene (DDE)), and five perfluoroalkyl substances (PFASs), and hair and cord blood mercury concentrations were measured. We used regression (single-pollutants) and structural equation models (SEMs) (multiple-pollutant analyses using latent constructs of OCs, PFASs and mercury) to estimate the associations with GDM and birth size measures, accounting for mediation and/or effect modification by GDM.RESULTS: Serum-DDE and hair-mercury concentrations were associated with GDM (adjusted OR per concentration doubling: 1.29; 0.95 CI: 0.94, 1.77 for DDE, and 0.79; 0.95 CI: 0.62, 0.99 for mercury), but in multiple pollutant-adjusted SEMs only a positive association between OC exposure and GDM remained significant (change in GDM odds per OC doubling: 0.45; 0.95 CI: 0.05, 0.86). PCB and overall OC exposure were positively associated with head circumference (SEM; mean change per OC doubling: 0.13cm; 0.95 CI, 0.01. 0.25). Overall PFAS exposure was inversely associated with birth weight (SEM; mean change per PFAS doubling: -169g; 0.95 CI: -359, 21), and for many single-PFASs we found a pattern of inverse associations with birth weight and head circumference in boys, and positive or null associations in girls. None of the environmental pollutants was associated with offspring length. GDM neither modified nor mediated the associations with birth size measures.CONCLUSIONS: We found associations with GDM and offspring birth size to be specific to the environmental pollutant or pollutant group. Associations with birth size measures appear to be independent of GDM occurrence.	●	●								-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献クラン①抽出	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
616	ヒト（生殖毒性）	Vélez, M. P.; Arbuckle, T. E.; Fraser, W. D.	Maternal exposure to perfluorinated chemicals and reduced fecundity: the MIREC study	2015	Hum Reprod. 2015 Mar;30(3):701-9. doi: 10.1093/humrep/deu350. Epub 2015 Jan 7.	Study question: What is the effect of maternal exposure to perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA) and perfluorohexane sulfonate (PFHxS) on female fecundity? Summary answer: Increasing concentrations of PFOA or PFHxS in maternal plasma were associated with reduced fecundability and infertility. What is known already: Perfluorinated chemicals (PFCs) are a group of synthetic compounds used in industrial production. There is a concern about the effect of PFCs on fecundity, as measured by time-to-pregnancy (TTP). Although some recent studies suggest that increasing concentrations of PFCs may decrease fecundity, divergence in the methodological approaches used to evaluate this association have prevented firm conclusions being reached. Study design, size, duration: The Maternal-Infant Research on Environmental Chemicals (MIREC) Study is a cohort study of 2,001 women recruited before 14 weeks of gestation in 10 cities across Canada between 2008 and 2011. Participants/materials, setting, methods: A questionnaire was administered and medical chart data and biospecimens were collected from participants. After excluding women who withdrew, those for whom data were incomplete, those whose pregnancies followed birth control failure, and accounting for male fertility, 1743 participants remained. TTP was defined as the number of months of unprotected intercourse needed to become pregnant in the current pregnancy, as self-reported in the first trimester of pregnancy. Plasma concentrations of PFOA, PFOS and PFHxS measured in the first trimester were considered as a surrogate of preconception exposure. Fecundability odds ratios (FORs) were estimated using Cox proportional hazard models for discrete time. FOR < 1 denote a longer TTP and FORs >1 denote a shorter TTP. The odds of infertility (TTP > 12 months or infertility treatment in the index pregnancy) were estimated using logistic regression. Each chemical concentration (ng/ml) was log-transformed and divided by its SD. Main results and the role of chance: The cumulative probabilities of pregnancy at 1, 6 and 12 months were 0.42 (95% confidence interval (CI) 0.40-0.45), 0.81 (95% CI 0.79-0.83) and 0.90 (95% CI 0.89-0.92), respectively. The mean maternal age was 32.8 (SD 5.0) years. The geometric means (ng/ml) of PFOA, PFOS and PFHxS were 1.66 (95% CI 1.61-1.71), 4.59 (95% CI 4.46-4.72) and 1.01 (95% CI 0.97-1.05), respectively. After adjustment for potential confounders, PFOA and PFHxS were associated with a 11 and 9% reduction in fecundability per one SD increase (FOR = 0.89; 95% CI 0.83-0.94; P < 0.001 for PFOA and FOR = 0.91; 95% CI 0.86-0.97; P = 0.002 for PFHxS), while no significant association was observed for PFOS (FOR = 0.96; 95% CI 0.91-1.02; P = 0.17). In addition, the odds of infertility increased by 31% per one SD increase of PFOA (odds ratio (OR) = 1.31; 95% CI 1.11-1.53; P = 0.001) and by 27% per one SD increase of PFHxS (OR = 1.27; 95% CI 1.09-1.48; P = 0.003), while no significant association was observed for PFOS (OR = 1.14; 95% CI 0.98-1.34; P = 0.09). Limitations, reasons for caution: Women with the highest concentrations of PFCs might have been excluded from the study if there is a causal association with infertility. The MIREC study did not assess concentrations of PFCs in males, semen quality, menstrual cycle characteristics or intercourse frequency. Wider implications of the findings: Our results add to the evidence that exposure to PFOA and PFHxS, even at lower levels than previously reported, may reduce fecundability. Study funding/competing interests: The MIREC study is supported by the Chemicals Management Plan of Health Canada, the Canadian Institutes for Health Research (CIHR, grant no. MOP - 81285) and the Ontario Ministry of the Environment. M.P.V. was supported by a CIHR Fellowship Award, and a CIHR-Quebec Training Network in Perinatal Research (QTNPR) Ph.D. scholarship. W.D.F. is supported by a CIHR Canada Research Chair	●	●	●	●			●		●	-		B	-
617	ヒト（生殖毒性）	Vested, Anne; Ramlau-Hansen, Cecilia Høst; Olsen, Sjurdur Frodi; Bonde, Jens Peter; Kristensen, Susanne Lund; Halldorsson, Thorhallur Ingi; Becher, Georg; Haug, Line Småstuen; Ernst, Emil Hagen; Toft, Gunnar	Associations of in utero exposure to perfluorinated alkyl acids with human semen quality and reproductive hormones in adult men	2013	Environ Health Perspect. 2013 Apr;121(4):453-8. doi: 10.1289/ehp.1205118. Epub 2013 Jan 28.	BACKGROUND: Perfluorinated alkyl acids (PFAAs), persistent chemicals with unique water-, dirt-, and oil-repellent properties, are suspected of having endocrine-disrupting activity. The PFAA compounds perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS) are found globally in humans; because they readily cross the placental barrier, in utero exposure may be a cause for concern. OBJECTIVES: We investigated whether in utero exposure to PFOA and PFOS affects semen quality, testicular volume, and reproductive hormone levels. METHODS: We recruited 169 male offspring (19-21 years of age) from a pregnancy cohort established in Aarhus, Denmark, in 1988-1989, corresponding to 37.6% of the eligible sons. Each man provided a semen sample and a blood sample. Semen samples were analyzed for sperm concentration, total sperm count, motility, and morphology, and blood samples were used to measure reproductive hormones. As a proxy for in utero exposure, PFOA and PFOS were measured in maternal blood samples from pregnancy week 30. RESULTS: Multivariable linear regression analysis suggested that in utero exposure to PFOA was associated with lower adjusted sperm concentration (ptrend = 0.01) and total sperm count (ptrend = 0.001) and with higher adjusted levels of luteinizing hormone (ptrend = 0.03) and follicle-stimulating hormone (ptrend = 0.01). PFOS did not appear to be associated with any of the outcomes assessed, before or after adjustment. CONCLUSIONS: The results suggest that in utero exposure to PFOA may affect adult human male semen quality and reproductive hormone levels.	●	●		●		●			●	-		B	-
618	ヒト（発生毒性）	Vesterholm Jensen, D.; Christensen, J.; Virtanen, H. E.; Skakkebæk, N. E.; Main, K. M.; Toppari, J.; Veje, C. W.; Andersson, A. M.; Nielsen, F.; Grandjean, P.; Jensen, T. K.	No association between exposure to perfluorinated compounds and congenital cryptorchidism: a nested case-control study among 215 boys from Denmark and Finland	2014	Reproduction. 2014 Mar 2;147(4):411-7. doi: 10.1530/REP-13-0444. Print 2014.	Geographical differences in the occurrence of diseases in male reproductive organs, including malformation in reproductive tract, between Denmark and Finland have been reported. The reason for these differences is unknown, but differences in exposure to chemicals with endocrine-disrupting abilities have been suggested. Among these chemicals are perfluoro-alkylated substances (PFASs), a group of water- and grease-repellent chemicals used in outdoor clothes, cookware, food packaging, and textiles. In this study, we, therefore, investigated differences in PFAS exposure levels between Denmark and Finland and the association between cord blood PFAS levels and congenital cryptorchidism. Boys from a joint ongoing prospective birth cohort study were included. We analyzed PFAS levels in cord blood serum samples collected from 29 Danish boys with congenital cryptorchidism, 30 healthy Danish matched controls recruited from 1997 to 2001, 30 Finnish cases, and 78 Finnish healthy matched controls recruited from 1997 to 1999 Additionally, 48 Finnish cases recruited from 2000 to 2002 were included. Perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS) were detected in all the 215 Danish and Finnish cord blood samples with significantly higher levels being observed in the Danish samples (medians: PFOA, 2.6 ng/ml and PFOS, 9.1 ng/ml) than in the Finnish samples (medians: PFOA, 2.1 ng/ml and PFOS, 5.2 ng/ml). We found no associations between cord blood PFOA and PFOS levels and congenital cryptorchidism after adjustment for confounders. Our data indicate that women in Denmark and Finland are generally exposed to PFOA and PFOS but there are differences in exposure levels between countries. We found no statistically significant association between cord blood PFOA and PFOS levels and congenital cryptorchidism; however, our study was small and larger studies are warranted.	●	●		●						-		B	-
619	ヒト（発生毒性）	Vuong, A.; Yolton, K.; Webster, G. M.; Sjodin, A.; Calafat, A. M.; Braun, J. M.; Dietrich, K.; Lanphear, B. P.; Chen, A.	Prenatal polybrominated diphenyl ether and perfluoroalkyl substance exposures and executive function in school-age children	2016	Environ Res. 2016 May;147:556-64. doi: 10.1016/j.envres.2016.01.008. Epub 2016 Jan 28.	Executive function is a critical behavioral trait rarely studied in relation to potential neurotoxicants. Prenatal exposure to polybrominated diphenyl ethers (PBDEs) and perfluoroalkyl substances (PFASs) has been associated with adverse neurodevelopment, but there is limited research on executive function. Data from 256 mother-child pairs in the Health Outcomes and Measures of the Environment Study, a prospective birth cohort (2003-2006, Cincinnati, OH), was used to examine maternal serum PBDEs and PFASs and executive function in children ages 5 and 8 years. Maternal serum PBDEs and PFASs were measured at 16±3 weeks gestation. Executive function was assessed with the parent-rated Behavior Rating Inventory of Executive Function (BRIEF), which yields composite measures: behavioral regulation index, metacognition index, and global executive composite. Higher BRIEF scores indicate executive function impairments. Linear mixed models and generalized estimating equations were used to estimate covariate-adjusted associations between PBDEs and PFASs and executive function. A 10-fold increase in BDE-153 was associated with poorer behavior regulation (β=3.23, 0.95 CI 0.60, 5.86). Higher odds of having a score ≥60 in behavior regulation (OR=3.92, 0.95 CI 1.76, 8.73) or global executive functioning (OR=2.34, 0.95 CI 1.05, 5.23) was observed with increased BDE-153. Each ln-unit increase in perfluorooctane sulfonate (PFOS) was associated with poorer behavior regulation (β=3.14, 0.95 CI 0.68, 5.61), metacognition (β=3.10, 0.95 CI 0.62, 5.58), and global executive functioning (β=3.38, 0.95 CI 0.86, 5.90). However, no association was observed between perfluorooctanoate (PFOA) and executive function. Prenatal exposures to BDE-153 and PFOS may be associated with executive function deficits in school-age children.	●	●	●	●						-		B	-
620	ヒト（発生毒性）	Vuong, A. M.; Yolton, K.; Wang, Z.; Xie, C.; Webster, G. M.; Ye, X.; Calafat, A. M.; Braun, J. M.; Dietrich, K. N.; Lanphear, B. P.; Chen, A.	Childhood perfluoroalkyl substance exposure and executive function in children at 8 years	2018	Environ Int. 2018 Oct;119:212-219. doi: 10.1016/j.envint.2018.06.028. Epub 2018 Jul 4.	BACKGROUND: Toxicological studies highlight the potential neurotoxicity of perfluoroalkyl substances (PFAS) during fetal development. However, few epidemiological studies have examined the impact of childhood PFAS on neurodevelopment.METHODS: We employed data from 208 children in the Health Outcomes and Measures of the Environment Study, a birth cohort (Cincinnati, OH), to examine associations of six serum PFAS concentrations measured at 3 and 8 years with executive function assessed at 8 years using the validated parent-completed Behavior Rating Inventory of Executive Function survey. We used multiple informant models to identify susceptible windows of neurotoxicity to PFAS and executive function. We investigated trajectories of PFAS concentrations and whether sex modified these associations.RESULTS: Each ln-increase in perfluorononanoate (PFNA) at 8 years was associated with a 3.4-point increase (95% CI 0.4, 6.3) in metacognition score, indicating poorer function. Children with PFNA above the median at 8 years had poorer global executive functioning compared to children with concentrations consistently below median levels (β = 6.5, 0.95 CI 0.2, 12.9). Higher concurrent PFNA was associated with poorer behavior regulation among males, while associations among females were null (pPFNA×sex = 0.018). Children with higher concurrent perfluorooctanoate (PFOA) had increased odds of being at risk of having clinical impairments in metacognition (OR = 3.18, 0.95 CI 1.17, 8.60). There were no associations between perfluorooctane sulfonate and perfluorohexane sulfonate and executive function.CONCLUSIONS: PFNA and PFOA at 8 years, but not 3 years, may be related to poorer executive function at 8 years. Results need to be confirmed in cohort studies with larger sample sizes.	●	●		●						-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献①ラン	文献②ラン
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
621	ヒト（生殖毒性）	Wang, B.; Zhang, R.; Jin, F.; Lou, H.; Mao, Y.; Zhu, W.; Zhou, W.; Zhang, P.; Zhang, J.	Perfluoroalkyl substances and endometriosis-related infertility in Chinese women	2017	Environ Int. 2017 May;102:207-212. doi: 10.1016/j.envint.2017.03.003. Epub 2017 Mar 7.	Endometriosis is one of the main causes for female infertility. Previous studies suggested that perfluoroalkyl substances (PFASs), a group of ubiquitous environmental chemicals with properties of endocrine disruption and reproductive toxicity, were risk factors for endometriosis but there lacks direct evidence on the possible role of PFASs in endometriosis-related infertility. To fill this gap, we examined the association between PFASs and endometriosis-related infertility among Chinese reproductive-age women in a case-control study, which comprised 157 surgically confirmed endometriosis cases and 178 controls seeking infertility treatment because of male reproductive dysfunction in 2014 and 2015 Blood specimens were collected at the enrollment and analyzed for ten PFASs. Logistic regression was utilized to estimate the adjusted odds ratios (OR) and 0.95 confidence intervals (CI) for individual PFAS compound. Plasma concentrations of perfluorobutane sulfonic acid (PFBS) were associated with an increased risk of endometriosis-related infertility (second vs. lowest tertile: OR=3.74, 0.95 CI: 2.04, 6.84; highest vs. lowest tertile: OR=3.04, 0.95 CI: 1.65, 5.57). This association remained consistent when we restricted to subjects with no previous pregnancy (second vs. lowest tertile: OR=2.91, 0.95 CI: 1.28, 6.61; highest vs. lowest tertile: OR=3.41, 0.95 CI: 1.52, 7.65) or to subjects without other gynecologic pathology (second vs. lowest tertile: OR=4.65, 0.95 CI: 2.21, 9.82; highest vs. lowest tertile: OR=3.36, 0.95 CI: 1.58, 7.15). Plasma concentrations of perfluoroheptanoic acid (PFHpA), perfluorohexane sulfonic acid (PFHxS) and perfluorononanoic acid (PFNA) were inversely associated with endometriosis-related infertility, but the associations were attenuated in the sensitivity analyses. Our preliminary evidence suggests that exposure to PFBS may increase the risk of female infertility due to endometriosis. Future prospective studies are necessary to confirm these findings.	●	●		●						-		B	-
622	ヒト（生殖毒性）	Wang, H.; Du, H.; Yang, J.; Jiang, H.; O, K.; Xu, L.; Liu, S.; Yi, J.; Qian, X.; Chen, Y.; Jiang, Q.; He, G.	PFOS, PFOA, estrogen homeostasis, and birth size in Chinese infants	2019	Chemosphere. 2019 Apr;221:349-355. doi: 10.1016/j.chemosphere.2019.01.061. Epub 2019 Jan 9.	Laboratory studies have suggested that perfluoroalkyl substances (PFASs) could affect fetal growth by disrupting estrogen homeostasis, but there are limited data for human. For this, 424 mother-infant pairs were selected from a cohort established in Hebei Province of North China in 2013 Two typical PFASs, perfluorooctyl sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA), and three typical estrogens, estrone (E1), β-estradiol (E2), and estriol (E3), were measured in cord serum. After adjusted for important covariates, serum PFOS was positively related to E1 and E3, but negatively related to E2. Serum PFOA was positively related to serum E1 and negatively related to head circumference at birth. Serum E2 was negatively related to head circumference, body weight, and body length at birth and serum E3 was positively related to body weight. Serum E3 mediated the relationship between serum PFOS and body weight. There were sex-specific differences for the associations between PFOS/PFOA and estrogens/birth size. These findings suggested that exposure to PFASs could affect estrogen homeostasis and fetal growth during pregnancy and that estrogens might mediate the association between exposure to PFASs and fetal growth.	●	●	●							-		B	-
623	ヒト（生殖毒性）	Wang, Y.; Adgent, M.; Su, P. H.; Chen, H. Y.; Chen, P. C.; Hsiung, C. A.; Wang, S. L.	Prenatal exposure to perfluorocarboxylic acids (PFCAs) and fetal and postnatal growth in the Taiwan maternal and infant cohort study	2016	Environ Health Perspect. 2016 Nov;124(11):1794-1800. doi: 10.1289/ehp.1509998. Epub 2016 Feb 19.	BACKGROUND: Perfluorocarboxylic acids (PFCAs) are environmentally and biologically persistent synthetic chemicals. PFCAs include perfluorooctanoic acid (PFOA; C8) and long-chain PFCAs (C9-C20). Studies examining long-chain PFCAs and fetal and postnatal growth are limited.OBJECTIVES: We investigated the associations of prenatal exposure to long-chain PFCAs with fetal and postnatal growth.METHODS: For 223 Taiwanese mothers and their term infants, we measured PFOA and four long-chain PFCAs (ng/mL) in third-trimester maternal serum; infant weight (kg), length and head circumference (cm) at birth; and childhood weight and height at approximately 2, 5, 8, and 11 years of age. For each sex, we used multivariable linear regression to examine associations between ln-transformed prenatal PFCAs and continuous infant measures, and logistic regression to examine small for gestational age (SGA). Linear mixed models were applied to prenatal PFCAs and childhood weight and height z-scores.RESULTS: In girls, prenatal perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDeA), perfluoroundecanoic acid (PFUnDA), and perfluorododecanoic acid (PFDoDA) concentrations were inversely associated with birth weight [e.g., βbirth weight (kg) = -0.06, 0.95 CI: -0.11, -0.01 per 1 ln-unit PFUnDA increase]; prenatal PFDeA and PFUnDA were associated with elevated odds of SGA; and PFDeA, PFUnDA, and PFDoDA were associated with lower average childhood height z-score. In boys, prenatal PFNA, and PFDoDA were associated with reductions in height at certain ages in childhood, but not with size at birth.CONCLUSIONS: Prenatal exposure to long-chain PFCAs may interfere with fetal and childhood growth in girls, and childhood growth in boys. Citation: Wang Y, Adgent M, Su PH, Chen HY, Chen PC, Hsiung CA, Wang SL. 2016 Prenatal exposure to perfluorocarboxylic acids (PFCAs) and fetal and postnatal growth in the Taiwan Maternal and Infant Cohort Study.	●	●	●	●			●			-		B	-
624	ヒト（発生毒性）	Wang, Y.; Rogan, W. J.; Chen, H. Y.; Chen, P. C.; Su, P. H.; Chen, H. Y.; Wang, S. L.	Prenatal exposure to perfluroalkyl substances and children's IQ: The Taiwan maternal and infant cohort study	2015	Int J Hyg Environ Health. 2015 Oct;218(7):639-44. doi: 10.1016/j.ijheh.2015.07.002. Epub 2015 Jul 9.	BACKGROUND: Perfluoroalkyl substances (PFASs) are a group of fluorinated organic substances that are widely used in consumer products and are often detectable in human tissues. Human studies on prenatal exposure to PFASs and neurodevelopment in children are few and inconsistent.METHODS: In the Taiwan Maternal and Infant Cohort Study, we collected serum samples from pregnant women during the third trimester and measured concentrations of 9 PFASs using a high performance liquid chromatography system. A subsample of their children was assessed with full scale intelligence quotient (FSIQ), verbal IQ (VIQ) and performance IQ (PIQ) at both age 5 (n=120) and 8 years (n=120). We used multivariate linear regression models to examine prenatal PFAS exposure in relation to IQ scores at each age period.RESULTS: Prenatal perfluoroundecanoic acid (PFUnDA) concentrations were inversely associated with children's PIQ scores at age 5 years, with an adjusted coefficient (β) of -1.6 (95% confidence interval [CI]: (-3.0, -0.2). When children reached 8 years, most of the prenatal PFASs showed inverse association with children's FSIQ, VIQ and PIQ scores. Among them, prenatal perfluorononanoic acid (PFNA) reached significance. Children with higher prenatal PFNA levels had lower VIQ with an adjusted β of -2.1 (95% CI: -3.9, -0.2).CONCLUSIONS: We found two prenatal PFAS exposure, both long-chain PFASs, in association with decreased IQ test scores in children. Our findings suggest more studies on long-chain PFASs and children's neurodevelopment.	●	●	●	●						-		B	-
625	ヒト（生殖毒性）	Whitworth, K. W.; Haug, L. S.; Baird, D. D.; Becher, G.; Hoppin, J. A.; Skjaerven, R.; Thomsen, C.; Eggesbo, M.; Travlos, G.; Wilson, R.; Longnecker, M. P.	Perfluorinated compounds and subfecundity in pregnant women	2012	Epidemiology. 2012 Mar;23(2):257-63. doi: 10.1097/EDE.0b013e31823b5031.	Background Perfluorinated compounds are ubiquitous pollutants; epidemiologic data suggest they may be associated with adverse health outcomes, including subfecundity. We examined subfecundity in relation to two perfluorinated compounds, perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA). Methods This case-control analysis included 910 women enrolled in the Norwegian Mother and Child Cohort Study in 2003 and 2004. Around gestational week 17, women reported their time to pregnancy and provided blood samples. Cases consisted of 416 women with a time to pregnancy greater than 12 months, considered subfecund. Plasma concentrations of perfluorinated compounds were analyzed using liquid chromatography-mass spectrometry. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were estimated for each pollutant quartile using logistic regression. Estimates were further stratified by parity. Results The median plasma concentration of PFOS was 13.0 ng/ml (interquartile range [IQR]=10.3-16.6 ng/ml) and of PFOA was 2.2 ng/ml (IQR=1.7-3.0 ng/ml). The relative odds of subfecundity among parous women was 2.1 (95% CI=1.2-3.8) for the highest PFOS quartile and 2.1 (1.0-4.0) for the highest PFOA quartile. Among nulliparous women, the respective relative odds were 0.7 (0.4-1.3) and 0.5 (0.2-1.2). Conclusion Previous studies suggest that the body burden of perfluorinated compounds decreases during pregnancy and lactation through transfer to the fetus and to breast milk. Afterwards, the body burden may rise again. Among parous women, increased body burden may be due to a long interpregnancy interval rather than the cause of a long time to pregnancy. Therefore, data from nulliparous women may be more informative regarding toxic effects of perfluorinated compounds. Our results among nulliparous women did not support an association with subfecundity.	●	●		●		●			●	-		B	-
626	ヒト（発生毒性）	Wikström, S.; Lin, P. I.; Lindh, C. H.; Shu, H.; Bornehag, C. G.	Maternal serum levels of perfluoroalkyl substances in early pregnancy and offspring birth weight	2019	Pediatr Res. 2020 May;87(6):1093-1099. doi: 10.1038/s41390-019-0720-1. Epub 2019 Dec 13.	BACKGROUND: Perfluoroalkyl substances (PFASs) are widespread, bioaccumulating, and persistent and show placental transfer. Emerging research indicates associations between prenatal exposure and low birth weight. The aim of this study was to assess the associations between first trimester exposure to PFASs and birth weight (BW) in the Swedish Environmental, Longitudinal, Mother and child, Asthma and allergy (SELMA) study and examine whether associations differ between girls and boys.METHODS: Eight PFASs were analyzed in maternal serum (median: 10 weeks of pregnancy). Associations between prenatal PFAS exposure and birth outcomes with BW, BW for gestational age, and birth small for gestational age (SGA) were assessed in 1533 infants, adjusted for potential confounders and stratified by sex.RESULTS: Increased maternal perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), and perfluoroundecanoic acid (PFUnDA) were associated with lower BW, lower BW for gestational age, and SGA birth. Associations were significant only in girls, where prenatal exposure in the upper quartile was associated with a 93-142-g lower BW when compared with that of the lowest quartile exposure. The associations were not mediated by effects on gestational age.CONCLUSIONS: We found associations between prenatal exposure for five different PFASs and birth weight, with more pronounced associations in girls than in boys.	●	●								-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
627	ヒト（生殖毒性）	Wikstrom, S.; Lindh, C. H.; Shu, H.; Bornehag, C. G.	Early pregnancy serum levels of perfluoroalkyl substances and risk of preeclampsia in Swedish women	2019	Sci Rep. 2019 Jun 24;9(1):9179. doi: 10.1038/s41598-019-45483-7.	Preeclampsia is a major cause of maternal and fetal morbidity. Emerging research shows an association with environmental exposures. The present aim was to investigate associations between early pregnancy serum levels of perfluoroalkyl substances (PFAS) and preeclampsia. Within the Swedish SELMA study, eight PFAS were measured at median 10 gestational weeks and cases of preeclampsia were postnatally identified from registers. Associations between individual PFAS and preeclampsia were assessed, adjusting for parity, age, weight and smoking. Out of 1773 women in the study group, 64 (3.6%), developed preeclampsia. A doubling of PFOS and PFNA exposure, corresponding to an inter-quartile increase, was associated with an increased risk for preeclampsia of about 38-53% respectively. Serum PFOS within the highest quartile was associated with an odds ratio of 2.68 (CI 95%: 1.17-6.12), equal to the increased risk associated with nulliparity, when compared to exposure in the first quartile. The same associations were identified, although with higher risk estimates, in analyses restricted to nulliparous women. For other PFAS, there were no associations. In conclusion and consistent with limited previous research only on PFOS, increasing serum levels of PFOS and PFNA during early pregnancy were associated with a clinically relevant risk of preeclampsia, adjusting for established confounders.	●	●							-		B	-
628	ヒト（発生毒性）	Workman, C. E.; Becker, A. B.; Azad, M. B.; Moraes, T. J.; Mandhane, P. J.; Turvey, S. E.; Subbarao, P.; Brook, J. R.; Sears, M. R.; Wong, C. S.	Associations between concentrations of perfluoroalkyl substances in human plasma and maternal, infant, and home characteristics in Winnipeg, Canada	2019	Environ Pollut. 2019 Jun;249:758-766. doi: 10.1016/j.envpol.2019.03.054. Epub 2019 Mar 21.	Perfluoroalkyl substances (PFASs) are known to be toxic, bioaccumulative, and persistent. However, exposure routes and toxic effects to humans are still widely unknown. Our objectives were to evaluate potential correlations between concentrations of PFASs in maternal plasma and infant cord blood with home characteristics and developmental effects, including wheezing. The concentrations of 17 PFASs were measured in plasma from prenatal women (n = 414), postnatal women (n = 247), and cord blood (n = 50) from a subset of participants in a population-based birth cohort in Winnipeg, Manitoba, Canada, using online solid phase extraction (SPE) with liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS). Multiple linear regression and principal component analysis (PCA) were used to evaluate possible associations with PFAS concentrations. Surveys were used to collect information regarding maternal characteristics (e.g. age, parity, duration of breastfeeding), infant characteristics (e.g. birth weight, birth length, head circumference, gestational age, and incidence of recurrent wheezing), and home characteristics (e.g. home age,carpet coverage in the most used room, presence of new furniture, or recent home renovations). PFASs in plasma were associated with maternal characteristics but not home characteristics or early childhood wheezing. PFASs were not associated with developmental effects, with the exception that perfluoroundecanoic acid (PFUA) was negatively associated with birth weight. Further studies investigating the potential influences of PFUA on birth weight are warranted.	●	●							-		B	-
629	ヒト（発生毒性）	Wu, H.; Yoon, M.; Verner, M. A.; Xue, J.; Luo, M.,an; Andersen, M. E.; Longnecker, M. P.; Clewell, H. J., III	Can the observed association between serum perfluoroalkyl substances and delayed menarche be explained on the basis of puberty-related changes in physiology and pharmacokinetics? Environ Int 82: 61-68	2015	Environ Int. 2015 Sep;82:61-8. doi: 10.1016/j.envint.2015.05.006. Epub 2015 May 29.	Background An association between serum levels of two perfluoroalkyl substances (PFAS) and delayed age at menarche was reported in a cross-sectional study of adolescents. Because perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) have half-lives of years, growth dilution and the development of a new route of excretion (menstruation) could account for some or all of the reported association. Objectives To assess how much of the epidemiologic association between PFAS and delayed menarche can be explained by the correlation of growth and maturation with PFAS body burden. Methods We developed a Monte Carlo (MC) physiologically-based pharmacokinetic (PBPK) model of PFAS to simulate plasma PFAS levels in a hypothetical female population aged 2 to 20 years old. Realistic distributions of physiological parameters as well as timing of growth spurts and menarche were incorporated in the model. The association between PFAS level and delayed menarche in the simulated data was compared with the reported association. Results The prevalence of menarche, distributions of age-dependent physiological parameters, and quartiles of serum PFAS concentrations in the simulated subjects were comparable to those reported in the epidemiologic study. The delay of menarche in days per natural log increase in PFAS concentrations in the simulated data were about one third as large as the observed values. Conclusion The reported relationship between PFAS and age at menarche appears to be at least partly explained by pharmacokinetics rather than a toxic effect of these substances.	●	●		●					-		B	-
630	ヒト（発生毒性）	Wu, Kusheng; Xu, Xijin; Peng, Lin; Liu, Junxiao; Guo, Yongyong; Huo, Xia	Association between maternal exposure to perfluorooctanoic acid (PFOA) from electronic waste recycling and neonatal health outcomes	2012	Environ Int. 2012 Nov 1;48:1-8. doi: 10.1016/j.envint.2012.06.018. Epub 2012 Jul 20.	OBJECTIVE: Perfluorooctanoic acid (PFOA) has applications in numerous industrial and consumer products. The widespread prevalence of PFOA in humans demonstrated in recent studies has drawn considerable interest from the public. We aimed to evaluate the exposure of mothers to PFOA and the potential hazards to neonates in a primitive electronic waste recycling area, Guiyu, China, and a control area, Chaonan, China. METHODS: Our investigation included analyses of maternal serum samples, health effect examinations, and other relevant factors. Questionnaires were administered and maternal serum samples were collected for 167 pregnant women. Solid phase extraction method was used for all analytical sample preparation, and analyses were completed using high performance liquid chromatography tandem mass spectrometry method. RESULTS: The PFOA concentration was higher in maternal serum samples from Guiyu than in samples from Chaonan (median 16.95, range 5.5-58.5 ng mL(-1); vs. 8.7, range 4.4-30.0 ng mL(-1); P<0.001). Residence in Guiyu, involvement in e-waste recycling, husband's involvement in e-waste and use of the family residence as workshop were significant factors contributing to PFOA exposure. Maternal PFOA concentrations were significantly different between normal births and adverse birth outcomes including premature delivery, term low birth weight, and stillbirths. After adjusting for potential confounders, PFOA was negatively associated with gestational age [per lg-unit: β=-15.99 days, 95% confidence interval (CI), -27.72 to -4.25], birth weight (per lg-unit: β=-267.3g, 95% CI, -573.27 to -37.18), birth length (per lg-unit: β=-1.91 cm, 95% CI, -3.31 to -0.52), and Apgar scores (per lg-unit: β=-1.37, 95% CI, -2.42 to -0.32), but not associated with ponderal index. CONCLUSIONS: Mothers from Guiyu were exposed to higher levels of PFOA than those from control areas. Prenatal exposure to PFOA was associated with decreased neonatal physical development and adverse birth outcomes.	●	●		●			●		-		C	-
631	ヒト（発生毒性）	Xiao, C.; Grandjean, P.; Valvi, D.; Nielsen, F.; Jensen, T. K.; Weihe, P.; Oulhote, Y.	Associations of exposure to perfluoroalkyl substances with thyroid hormone concentrations and birth size	2020	J Clin Endocrinol Metab. 2020 Mar 1;105(3):735-745. doi: 10.1210/clinem/dgz147.	BACKGROUND: Adequate thyroid function during pregnancy is essential for optimal fetal growth. Gestational exposure to perfluoroalkyl substances (PFASs) can negatively affect birth size and disrupt maternal and neonatal thyroid function, although the interrelationship is unclear.OBJECTIVE: We aimed to quantify the associations between maternal serum-PFAS concentrations and birth weight, birth length, and cranial circumference. We also aimed to estimate associations between PFAS and thyroid hormone (TH) concentrations, thereby elucidating whether THs potentially mediate the associations between PFAS concentrations and birth size.METHODS: We studied a population-based prospective cohort of 172 mother-singleton pairs from the Faroe Islands. Twelve PFAS were measured in maternal serum obtained at 34 weeks of gestation. THs were measured in maternal and cord serum. Associations between PFAS concentrations and birth size and TH concentrations were estimated using multivariable linear regressions. Sex-stratified analyses along with a mediation analysis were performed to estimate potential mediating effects of THs in the association between PFAS and birth outcomes.RESULTS: Several PFASs were negatively associated with birth weight, length, and head circumference, and a general positive association between maternal serum-PFASs and cord serum-thyroid stimulating hormone was found. For instance, a doubling in perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) was associated with a 0.53 (95% CI: 18%, 99%) and 0.4 (95% CI: 8%, 81%) increases in thyroid stimulating hormone concentrations, respectively. There was little evidence of sexually dimorphic associations. Overall, THs were not found to mediate associations between PFASs and birth size.CONCLUSION: In this study, several PFASs were negatively associated with birth size and increased THs, which however did not explain lower birth weight among children exposed to PFAS.	●	●							-		B	-
632	ヒト（発生毒性）	Xu, C.; Yin, S.; Liu, Y.; Chen, F.; Zhong, Z.; Li, F.; Liu, K.; Liu, W.	Prenatal exposure to chlorinated polyfluoroalkyl ether sulfonic acids and perfluoroalkyl acids: Potential role of maternal determinants and associations with birth outcomes	2019	J Hazard Mater. 2019 Dec 15;380:120867. doi: 10.1016/j.jhazmat.2019.120867. Epub 2019 Jul 11.	Transplacental exposure to per/polyfluoroalkyl substances (PFASs) may impact fetal growth, but published evidence are still sparse and not in agreement. Moreover, little is known on the occurrence of emerging chlorinated polyfluorinated ether sulfonates (Cl-PFESAs, 6:2 and 8:2) in maternal-neonatal population. This study investigated eleven PFASs by analyzing 98 cord samples from Hangzhou, China. All target compounds can be transported across placenta, with highest median concentrations of 4.07, 1.05 and 0.731 ng/mL for PFOS, PFOA, and 6:2 Cl-PFESA. Older ages and higher pre-pregnancy BMI were associated with higher cord PFASs concentration; being primiparous was also significantly associated. Notably, after adjusting for potential confounders, PFOS was negatively associated with birth weight (β = -417.3 g, 0.95 CI: -742.1, -92.4, p = 0.011, per a log10 unit increase in exposure) and ponderal index (β = -0.005 g/cm3, 0.95 CI: -0.008, -0.002, p = 0.000). PFOS and PFHxS were also indicated to be associated with small for gestational age birth (SGA) (p < 0.05). Although no evidence of association was observed between Cl-PFESAs and birth outcomes in this study, the bioaccumulative properties and development toxicity of Cl-PFESAs deserve continuous concern.	●	●							-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
633	ヒト（発生毒性）	Yeung, E. H.; Bell, E. M.; Sundaram, R.; Ghassabian, A.; Ma, W.; Kannan, K.; Louis, G. M.	Examining endocrine disruptors measured in newborn dried blood spots and early childhood growth in a prospective cohort	2019	Obesity (Silver Spring). 2019 Jan;27(1):145-151. doi: 10.1002/oby.22332.	OBJECTIVE: The goal of this study was to determine whether newborn concentrations of perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), and bisphenol A (BPA) are associated with early childhood growth.METHODS: A total of 1954 singletons and 966 twins from the Upstate KIDS Study (born 2008-2010) were included in this study. Newborn dried blood spot concentrations of PFOS, PFOA, and BPA were quantified by liquid chromatography tandem mass spectrometry. Children's weight and height were reported from birth through 3 years of age. Repeated measures were modeled using generalized linear mixed models.RESULTS: PFOS and PFOA were associated with lower BMI (-0.078 kg/m2 [-0.12 to -0.038] and -0.076 kg/m2 [-0.17 to -0.051] per 1 standard deviation increase in log PFOS and PFOA, respectively) and not with early obesity among singletons. Inconsistent associations were observed for twins. BPA levels were higher among neonates with a neonatal intensive care unit stay (P < 0.001), making associations difficult to interpret.CONCLUSIONS: Perfluorinated alkyl substances did not exhibit obesogenic associations with early measures of childhood growth. Blood-based BPA measures are limited by the nonpersistent nature of the chemical, and unknown sources from hospital settings may present only transient exposures.	●	●							-		B	-
634	ヒト（発生毒性）	Zhang, C.; Sundaram, R.; Maisog, J.; Calafat, A. M.; Barr, D. B.; Buck Louis, G. M.	A prospective study of prepregnancy serum concentrations of perfluorochemicals and the risk of gestational diabetes	2015	Fertil Steril. 2015 Jan;103(1):184-9. doi: 10.1016/j.fertnstert.2014.10.001. Epub 2014 Oct 22.	OBJECTIVE: To examine preconception serum concentrations of perfluorooctanoic acid (PFOA) and six other PFCs in relation to gestational diabetes (GDM) risk.DESIGN: Prospective cohort with longitudinal follow-up.SETTING: Not applicable.PATIENT(S): Among 501 women recruited upon discontinuing contraception for the purpose of becoming pregnant, 258 -0.51 became pregnant and were eligible for the study, of which 28 -0.11 reported having physician-diagnosed GDM during follow-up.INTERVENTION(S): None.MAIN OUTCOME MEASURE(S): The odds ratios (ORs) and 0.95 confidence intervals (CIs) of GDM associated with each standard deviation (SD) increment of preconception serum PFOA concentration (ng/mL, log-transformed) and six other PFCs were estimated with the use of logistic regression after adjusting for age, prepregnancy body mass index, smoking, and parity conditional on gravidity.RESULT(S): Preconception geometric mean (95% CI) PFOA concentrations (in ng/mL) were higher for women with than without GDM (3.94 [3.15-4.93] vs. 3.07 [2.83-3.12], respectively). Each SD increment in PFOA was associated with a 1.87-fold increased GDM risk (adjusted OR 1.86 [95% CI 1.14-3.02]). A slightly increased risk associated with each SD increment for the six other PFCs was observed as well (all ORs >1.0, range 1.06-1.27), although the associations were not statistically significant.CONCLUSION(S): Our findings suggested that higher environmentally relevant concentrations of PFOA were significantly associated with an increased risk of GDM. If corroborated, these findings may be suggestive of a possible environmental etiology for GDM.	●	●		●					-		B	-
635	ヒト（発生毒性）	Zhang, H.; Yolton, K.; Webster, G. M.; Ye, X.; Calafat, A. M.; Dietrich, K. N.; Xu, Y.; Xie, C.; Braun, J. M.; Lanphear, B. P.; Chen, A.	Prenatal and childhood perfluoroalkyl substances exposures and children's reading skills at ages 5 and 8 years	2018	Environ Int. 2018 Feb;111:224-231. doi: 10.1016/j.envint.2017.11.031. Epub 2017 Dec 20.	BACKGROUND: Exposure to perfluoroalkyl substances (PFASs) may impact children's neurodevelopment.OBJECTIVE: To examine the association of prenatal and early childhood serum PFAS concentrations with children's reading skills at ages 5 and 8years.METHODS: We used data from 167 mother-child pairs recruited during pregnancy (2003-2006) in Cincinnati, OH, quantified prenatal serum PFAS concentrations at 16±3weeks of gestation and childhood sera at ages 3 and 8years. We assessed children's reading skills using Woodcock-Johnson Tests of Achievement III at age 5years and Wide Range Achievement Test-4 at age 8years. We used general linear regression to quantify the covariate-adjusted associations between natural log-transformed PFAS concentrations and reading skills, and used multiple informant model to identify the potential windows of susceptibility.RESULTS: Median serum PFASs concentrations were PFOS>PFOA>PFHxS>PFNA in prenatal, 3-year, and 8-year children. The covariate-adjusted general linear regression identified positive associations between serum PFOA, PFOS and PFNA concentrations and children's reading scores at ages 5 and 8years, but no association between any PFHxS concentration and reading skills. The multiple informant model showed: a) Prenatal PFOA was positively associated with higher children's scores in Reading Composite (β: 4.0, 0.95 CI: 0.6, 7.4 per a natural log unit increase in exposure) and Sentence Comprehension (β: 4.2, 0.95 CI: 0.5, 8.0) at age 8years; b) 3-year PFOA was positively associated with higher children's scores in Brief Reading (β: 7.3, 0.95 CI: 0.9, 13.8), Letter Word Identification (β: 6.6, 0.95 CI: 1.1, 12.0), and Passage Comprehension (β: 5.9, 0.95 CI: 1.5, 10.2) at age 5years; c) 8-year PFOA was positively associated with higher children's Word Reading scores (β: 5.8, 0.95 CI: 0.8, 10.7) at age 8years. Prenatal PFOS and PFNA were positively associated with children's reading abilities at age 5years, but not at age 8years; 3-year PFOS and PFNA were positively associated with reading scores at age 5years. But PFHxS concentrations, at any exposure windows, were not associated with reading skills.CONCLUSION: Prenatal and childhood serum PFOA, PFOS and PFNA concentrations were positively associated with better children's reading skills at ages 5 and 8years, but no association was found between serum PFHxS and reading skills.	●	●		●					-		B	-
636	ヒト（生殖毒性）	Zhou, W.; Zhang, L.; Tong, C.; Fang, F.; Zhao, S.; Tian, Y.; Tao, Y.; Zhang, J.	Plasma perfluoroalkyl and polyfluoroalkyl substances concentration and menstrual cycle characteristics in preconception women	2017	Environ Health Perspect. 2017 Jun 22;125(6):067012. doi: 10.1289/EHP1203.	BACKGROUND: Perfluoroalkyl and polyfluoroalkyl substances (PFASs) are persistent synthetic chemicals that are widely used in industrial applications and often detectable in humans. In rats, PFASs can interfere with the estrous cycle. In humans, menstruation has been viewed as a proxy of female fecundity, and periodic menstruation plays a critical role in endometrial sloughing in the absence of pregnancy and in preparing for embryo implantation.OBJECTIVES: We investigated the association between PFAS exposure and menstrual cycle characteristics in women who plan to become pregnant.METHODS: Plasma level of 10 PFASs was measured in 950 women who were attempting to become pregnant and recruited in two preconception care clinics in Shanghai, China, from August 2013 to April 2015 Information on menstrual cycle characteristics was collected by questionnaires. Associations between PFAS levels and menstrual cycle regularity, length, and bleeding volume were examined using multiple logistic regression models.RESULTS: Pre-pregnant women with higher levels of log-transformed perfluorooctanate (PFOA), perfluorooctane sulfonate (PFOS), perfluorononanoic acid (PFNA), and perfluorohexanesulfonate (PFHxS) had increased odds of self-reported history of irregular menstrual cycle [(95% CI: 1.08, 2.15); (95% CI: 0.98, 1.70); (95% CI: 1.03, 2.07); (95% CI: 1.17, 2.77)] and long menstrual cycle [(95% CI: 1.06, 2.10); (95% CI: 1.02, 1.75); (95% CI: 1.05, 2.11); (95% CI: 1.13, 2.65)]. Log-transformed PFOA, PFOS, PFNA. and PFHxS levels were negatively associated with self-reported history of menorrhagia [(95% CI: 0.21, 0.65); (95% CI: 0.37, 0.90); (95% CI: 0.26, 0.86); (95% CI: 0.06, 0.36)].CONCLUSIONS: Certain PFASs are associated with abnormal menstruation in humans.	●	●							-		B	-
637	ヒト（生殖毒性）	Zhou, Y.; Hu, L. W.; Qian, Z. M.; Chang, J. J.; King, C.; Paul, G.; Lin, S.; Chen, P. C.; Lee, Y. L.; Dong, G. H.	Association of perfluoroalkyl substances exposure with reproductive hormone levels in adolescents: By sex status	2016	Environ Int. 2016 Sep;94:189-195. doi: 10.1016/j.envint.2016.05.018. Epub 2016 May 31.	Polyfluoroalkyl substances (PFASs) are a group of common chemicals that ubiquitously exist in wildlife and humans. However, few studies have researched the effect of PFASs on reproductive hormones in adolescents. To provide information in this regard, we recruited 225 Taiwanese adolescents aged 13-15years from 2009 to 2010 to investigate the relationship between serum PFASs (PFOS, PFOA, PFBS, PFDA, PFDoA, PFHxA, PFHxS, PFNA and PFTA) and reproductive hormone concentrations using a cross-sectional study design. Results showed PFOS and PFTA levels were highest among the PFASs, with a median concentrations of 29.9 (interquartile range: 13.0-43.8) ng/mL and 6 (0.6-25.9) ng/mL in males, and a median concentrations of 28.8 (14.8-42.6) ng/mL and 4.5 (0.3-18.4) ng/mL in females. After adjustment for confounding factors, nonsignificant associations between PFASs and reproductive hormone were found except for PFNA with ln(estradiol) (β=0.2060, 95%CI: 0.0016, 0.4105). When stratified by sex, more significant associations were found in males than in females. Among males, PFASs were negatively associated with ln(testosterone) level for PFOS (β=-0.0029, 95%CI: -0.0055, -0.0003), PFDA (β=-0.2565, 95%CI: -0.4135, -0.0994), PFHxA (β=-0.3095, 95%CI: -0.5942, -0.0248), and PFNA (β=-0.4233, 95%CI: -0.6998, -0.1467). Furthermore, male participant ln(estradiol) levels were positively associated with PFOA (β=0.0921, 95%CI: 0.0186, 0.1656), and PFHxS (β=0.0462, 95%CI: 0.0020, 0.0905). Among females, a significant relationship was found only for PFDoA with ln(testosterone) (β=-0.0119, 95%CI: -0.0227, -0.0010). In conclusion, this study showed higher levels of PFASs coincide with lower testosterone and higher estradiol levels, and more significant associations of PFASs with reproductive hormone were found in males than in females.	●	●		●					-		B	-
638	ヒト（生殖毒性）	Buck Louis, Germaine M; Sundaram, Rajeshwari; Schisterman, Enrique F; Sweeney, Anne M; Lynch, Courtney D; Gore-Langton, Robert E; Maisog, José; Kim, Sungduk; Chen, Zhen; Barr, Dana B	Persistent environmental pollutants and couple fecundity: the LIFE study	2013	Environ Health Perspect. 2013 Feb;121(2):231-6. doi: 10.1289/ehp.1205301. Epub 2012 Nov 14.	BACKGROUND: Evidence suggesting that persistent environmental pollutants may be reproductive toxicants underscores the need for prospective studies of couples for whom exposures are measured. OBJECTIVES: We examined the relationship between selected persistent pollutants and couple fecundity as measured by time to pregnancy. METHODS: A cohort of 501 couples who discontinued contraception to become pregnant was prospectively followed for 12 months of trying to conceive or until a human chorionic gonadotrophin (hCG) test confirmed pregnancy. Couples completed daily journals on lifestyle and provided biospecimens for the quantification of 9 organochlorine pesticides, 1 polybrominated biphenyl, 10 polybrominated diphenyl ethers, 36 polychlorinated biphenyls (PCBs), and 7 perfluorochemicals (PFCs) in serum. Using Cox models for discrete time, we estimated fecundability odds ratios (FORs) and 95% CIs separately for each partner's concentrations adjusting for age, body mass index, serum cotinine, serum lipids (except for PFCs), and study site (Michigan or Texas); sensitivity models were further adjusted for left truncation or time off of contraception (≤ 2 months) before enrollment. RESULTS: The adjusted reduction in fecundability associated with standard deviation increases in log-transformed serum concentrations ranged between 18% and 21% for PCB congeners 118, 167, 209, and perfluorooctane sulfonamide in females; and between 17% and 29% for p,p′-DDE and PCB congeners 138, 156, 157, 167, 170, 172, and 209 in males. The strongest associations were observed for PCB 167 (FOR 0.79; 95% CI: 0.64, 0.97) in females and PCB 138 (FOR = 0.71; 95% CI: 0.52, 0.98) in males. CONCLUSIONS: In this couple-based prospective cohort study with preconception enrollment and quantification of exposures in both female and male partners, we observed that a subset of persistent environmental chemicals were associated with reduced fecundity.			●	●					-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
639	ヒト（生殖毒性）	Chen, Mei-Huei; Ha, Eun-Hee; Wen, Ting-Wen; Su, Yi-Ning; Lien, Guang-Wen; Chen, Chia-Yang; Chen, Pau-Chung; Hsieh, Wu-Shiun	Perfluorinated compounds in umbilical cord blood and adverse birth outcomes	2012	PLoS One. 2012;7(8):e42474. doi: 10.1371/journal.pone.0042474. Epub 2012 Aug 3.	BACKGROUND: Previous animal studies have shown that perfluorinated compounds (PFCs) have adverse impacts on birth outcomes, but the results have been inconclusive in humans. We investigated associations between prenatal exposure to perfluorooctanoic acid (PFOA), perfluorooctyl sulfonate (PFOS), perfluorononanoic acid (PFNA), and perfluoroundecanoic acid (PFUA) and birth outcomes. METHODS: In total, 429 mother-infant pairs were recruited from the Taiwan Birth Panel Study (TBPS). Demographic data were obtained by interviewing mothers using a structured questionnaire and birth outcomes were extracted from medical records. Cord blood was collected for PFOA, PFOS, PFNA, and PFUA analysis by ultra-high-performance liquid chromatography/tandem mass spectrometry. RESULTS: The geometric mean (standard deviation) levels of PFOA, PFOS, PFNA, and PFUA in cord blood plasma were 1.84 (2.23), 5.94 (1.95), 2.36(4.74), and 10.26 (3.07) ng/mL, respectively. Only PFOS levels were found to be inversely associated with gestational age, birth weight, and head circumference [per ln unit: adjusted β (95% confidence interval, CI) = -0.37 (-0.60, -0.13) wks, -110.2 (-176.0, -44.5) gm and -0.25 (-0.46, -0.05) cm]. Additionally, the odds ratio of preterm birth, low birth weight, and small for gestational age increased with PFOS exposure [per ln unit: adjusted odds ratio (OR) (95%CI) = 2.45 (1.47, 4.08), 2.61(0.85, 8.03) and 2.27 (1.25, 4.15)]. When PFOS levels were divided into quartiles, a dose-response relation was observed. However, PFOA, PFNA, and PFUA were not observed to have any convincing impact on birth outcomes. CONCLUSIONS: An adverse dose-dependent association was observed between prenatal PFOS exposure and birth outcomes. However, no associations were found for the other examined PFCs.			●	●			●			-		B	-
640	ヒト（代謝）	Halldorsson, Thorhallur I; Rytter, Dorte; Haug, Line Småstuen; Bech, Bodil Hammer; Danielsen, Inge; Becher, Georg; Henriksen, Tine Brink; Olsen, Sjurdur F	Prenatal exposure to perfluorooctanoate and risk of overweight at 20 years of age: a prospective cohort study	2012	Environ Health Perspect. 2012 May;120(5):668-73. doi: 10.1289/ehp.1104034. Epub 2012 Feb 3.	BACKGROUND: Perfluoroalkyl acids are persistent compounds used in various industrial -applications. Of these compounds, perfluorooctanoate (PFOA) is currently detected in humans worldwide. A recent study on low-dose developmental exposure to PFOA in mice reported increased weight and elevated biomarkers of adiposity in postpubertal female offspring. OBJECTIVE: We examined whether the findings of increased weight in postpubertal female mice could be replicated in humans. METHODS: A prospective cohort of 665 Danish pregnant women was recruited in 1988-1989 with offspring follow-up at 20 years. PFOA was measured in serum from gestational week 30. Offspring body mass index (BMI) and waist circumference were recorded at follow-up (n = 665), and biomarkers of adiposity were quantified in a subset (n = 422) of participants. RESULTS: After adjusting for covariates, including maternal pre-pregnancy BMI, smoking, education, and birth weight, in utero exposure to PFOA was positively associated with anthropometry at 20 years in female but not male offspring. Adjusted relative risks comparing the highest with lowest quartile (median: 5.8 vs. 2.3 ng/mL) of maternal PFOA concentration were 3.1 [95% confidence interval (CI): 1.4, 6.9] for overweight or obese (BMI ≥ 25 kg/m2) and 3.0 (95% CI: 1.3, 6.8) for waist circumference > 88 cm among female offspring. This corresponded to estimated increases of 1.6 kg/m2 (95% CI: 0.6, 2.6) and 4.3 cm (95% CI: 1.4, 7.3) in average BMI and waist circumference, respectively. In addition, maternal PFOA concentrations were positively associated with serum insulin and leptin levels and inversely associated with adiponectin levels in female offspring. Similar associations were observed for males, although point estimates were less precise because of fewer observations. Maternal perfluorooctane sulfonate (PFOS), perfluorooctane sulfonamide (PFOSA), and perfluorononanoate (PFNA) concentrations were not independently associated with offspring anthropometry at 20 years. CONCLUSIONS: Our findings on the effects of low-dose developmental exposures to PFOA are in line with experimental results suggesting obesogenic effects in female offspring at 20 years of age.			●	●	●	●	●			-	1	A	-
641	ヒト（生殖毒性）	Hamm, Michele P; Cherry, Nicola M; Chan, Emily; Martin, Jonathan W; Burstyn, Igor	Maternal exposure to perfluorinated acids and fetal growth	2010	J Expo Sci Environ Epidemiol.;20(7):589-97. doi: 10.1038/jes.2009.57. Epub 2009 Oct 28.	The widespread detection of perfluorinated acids (PFAs) in humans and known developmental toxicity in animals has raised concern about their potential effects on human reproductive health. Our objective was to determine whether increasing maternal exposure to PFAs is associated with adverse effects on fetal growth and length of gestation in women giving birth in Alberta, Canada. We examined the concentrations of perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), and perfluorohexane sulfonate (PFHxS) in a cohort of 252 pregnant women who gave birth to live singletons. Each of the women had undergone an early second trimester prenatal screen, and her serum was analyzed for PFA concentrations. Data on infant and maternal variables were collected from the delivery record completed at birth. Adjusted changes in birth weight per natural log (ng/ml) of PFOA (median 1.5 ng/ml), PFHxS (median 0.97 ng/ml), and PFOS (median 7.8 ng/ml) were -37.4 g (95% confidence interval (CI): -86.0 to 11.2 g), 21.9 g (-23.4 to 67.2 g), and 31.3 g (-43.3 to 105.9 g), respectively. Mean birth weight z-score, standardized for gestational age and gender, length of gestation, and risk of preterm birth did not appear to be influenced by maternal PFA exposure. When PFA concentrations were divided into tertiles, similar patterns were observed. These results suggest that maternal PFA exposure has no substantial effect on fetal weight and length of gestation at the concentrations observed in this population.			●	●	●	●	●			-		B	-
642	ヒト（生殖毒性）	Johnson, Paula I; Sutton, Patrice; Atchley, Dylan S; Koustas, Erica; Lam, Juleen; Sen, Saunak; Robinson, Karen A; Axelrad, Daniel A; Woodruff, Tracey J	The navigation guide-evidence-based medicine meets environmental health: systematic review of human evidence for PFOA effects on fetal growth	2014	Environ Health Perspect. 2014 Oct;122(10):1028-39. doi: 10.1289/ehp.1307893. Epub 2014 Jun 25.	BACKGROUND: The Navigation Guide methodology was developed to meet the need for a robust method of systematic and transparent research synthesis in environmental health science. We conducted a case study systematic review to support proof of concept of the method. OBJECTIVE: We applied the Navigation Guide systematic review methodology to determine whether developmental exposure to perfluorooctanoic acid (PFOA) affects fetal growth in humans. METHODS: We applied the first 3 steps of the Navigation Guide methodology to human epidemiological data: 1) specify the study question, 2) select the evidence, and 3) rate the quality and strength of the evidence. We developed a protocol, conducted a comprehensive search of the literature, and identified relevant studies using prespecified criteria. We evaluated each study for risk of bias and conducted meta-analyses on a subset of studies. We rated quality and strength of the entire body of human evidence. RESULTS: We identified 18 human studies that met our inclusion criteria, and 9 of these were combined through meta-analysis. Through meta-analysis, we estimated that a 1-ng/mL increase in serum or plasma PFOA was associated with a -18.9 g (95% CI: -29.8, -7.9) difference in birth weight. We concluded that the risk of bias across studies was low, and we assigned a "moderate" quality rating to the overall body of human evidence. CONCLUSION: On the basis of this first application of the Navigation Guide systematic review methodology, we concluded that there is "sufficient" human evidence that developmental exposure to PFOA reduces fetal growth.			●	●		●	●			-		B	-
643	ヒト（発生毒性）	Maisonet, Mildred; Terrell, Metrecia L; McGeehin, Michael A; Christensen, Krista Yorita; Holmes, Adrianne; Calafat, Antonia M; Marcus, Michele	Maternal concentrations of polyfluoroalkyl compounds during pregnancy and fetal and postnatal growth in British girls	2012	Environ Health Perspect. 2012 Oct;120(10):1432-7. doi: 10.1289/ehp.1003096. Epub 2012 Aug 30.	BACKGROUND: Prenatal exposures to polyfluoroalkyl compounds (PFCs) may be associated with adverse changes in fetal and postnatal growth. OBJECTIVE: We explored associations of prenatal serum concentrations of perfluorooctane sulfonate (PFOS), perfluorooctanoate (PFOA), and perfluorohexane sulfonate (PFHxS) with fetal and postnatal growth in girls. METHODS: We studied a sample of 447 singleton girls and their mothers participating in the Avon Longitudinal Study of Parents and Children (ALSPAC). Data on weight and length were obtained at birth and at 2, 9, and 20 months. Serum samples were obtained in 1991-1992, from mothers during pregnancy. We explored associations between prenatal PFC concentrations and weight at birth as well as longitudinal changes in weight-for-age SD scores between birth and 20 months. RESULTS: PFOS (median, 19.6 ng/mL), PFOA (median, 3.7 ng/mL), and PFHxS (median, 1.6 ng/mL) were detected in 100% of samples. On average, girls born to mothers with prenatal concentrations of PFOS in the upper tertile weighed 140 g less [95% confidence interval (CI): -238, -42] at birth than girls born to mothers with concentrations in the lower tertile in adjusted models. Similar patterns were seen for PFOA (-133 g; 95% CI: -237, -30) and PFHxS (-108 g; 95% CI: -206, -10). At 20 months, however, girls born to mothers with prenatal concentrations of PFOS in the upper tertile weighed 580 g more (95% CI: 301, 858) when compared with those in the lower tertile. No differences in weight were found for PFOA and PFHxS. CONCLUSIONS: Girls with higher prenatal exposure to each of the PFCs examined were smaller at birth than those with lower exposure. In addition, those with higher exposure to PFOS were larger at 20 months.			●	●	●	●	●			-		B	-
644	ヒト（免疫毒性）	Okada, Emiko; Sasaki, Seiko; Saijo, Yasuaki; Washino, Noriaki; Miyashita, Chihiro; Kobayashi, Sumitaka; Konishi, Kanae; Ito, Yoichi M; Ito, Rie; Nakata, Ayako; Iwasaki, Yusuke; Saito, Koichi; Nakazawa, Hiroyuki; Kishi, Reiko	Prenatal exposure to perfluorinated chemicals and relationship with allergies and infectious diseases in infants	2012	Environ Res. 2012 Jan;112:118-25. doi: 10.1016/j.envres.2011.10.003. Epub 2011 Oct 24.	BACKGROUND: Recent studies have shown effects of prenatal exposure to perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) on infants in the general environmental levels. Laboratory animal studies have shown that exposure to PFOS and PFOA is associated with immunotoxic effects. OBJECTIVES: To investigate the relationship between maternal PFOS and PFOA levels and infant allergies and infectious diseases during the first 18 months of life. Cord blood immunoglobulin (Ig) E levels were also evaluated. METHODS: We conducted a prospective cohort study of pregnant women from 2002 to 2005 in Sapporo, Japan. Maternal PFOS and PFOA levels were measured in relation to cord blood IgE concentrations (n=231) and infant allergies and infectious diseases (n=343). Characteristics of mothers and their infants were obtained from self-administered questionnaires and medical records. Development of infant allergies and infectious diseases was determined from self-administered questionnaires at 18 months of age. Concentrations of PFOS and PFOA in maternal serum and concentrations of IgE in umbilical cord serum at birth were measured. RESULTS: Cord blood IgE levels decreased significantly with high maternal PFOA concentration among female infants. However, there were no significant associations among maternal PFOS and PFOA levels and food allergy, eczema, wheezing, or otitis media in the 18 month-old infants (adjusted for confounders). CONCLUSIONS: Although cord blood IgE level decreased significantly with high maternal PFOA levels among female infants, no relationship was found betweenmaternal PFOS and PFOA levels and infant allergies and infectious diseases at age in 18 months.			●	●	●	●				-	1	A	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献ランク①	文献ランク②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
645	ヒト（生殖毒性）	Robledo, Candace A; Yeung, Edwina; Mendola, Pauline; Sundaram, Rajeshwari; Maisog, Jose; Sweeney, Anne M; Barr, Dana Boyd; Louis, Germaine M Buck	Preconception maternal and paternal exposure to persistent organic pollutants and birth size: the LIFE study	2015	Environ Health Perspect. 2015 Jan;123(1):88-94. doi: 10.1289/ehp.1308016. Epub 2014 Aug 5.	BACKGROUND: Persistent organic pollutants (POPs) are developmental toxicants, but the impact of both maternal and paternal exposures on offspring birth size is largely unexplored. OBJECTIVE: We examined associations between maternal and paternal serum concentrations of 63 POPs, comprising five major classes of pollutants, with birth size measures. METHODS: Parental serum concentrations of 9 organochlorine pesticides, 1 polybrominated biphenyl (PBB), 7 perfluoroalkyl chemicals (PFCs), 10 polybrominated diphenyl ethers (PBDEs), and 36 polychlorinated biphenyls (PCBs) were measured before conception for 234 couples. Differences in birth weight, length, head circumference, and ponderal index were estimated using multiple linear regression per 1-SD increase in natural log-transformed (ln-transformed) chemicals. Models were estimated separately for each parent and adjusted for maternal age, maternal prepregnancy body mass index (kilograms per meter squared) and other confounders, and all models included an interaction term between infant sex and each chemical. RESULTS: Among girls (n = 117), birth weight was significantly lower (range, 84-195 g) in association with a 1-SD increase in ln-transformed maternal serum concentrations of DDT, PBDE congeners 28 and 183, and paternal serum concentrations of PBDE-183 and PCB-167. Among boys (n = 113), maternal (PCBs 138, 153, 167, 170, 195, and 209 and perfluorooctane sulfonamide) and paternal (PCBs 172 and 195) serum concentrations of several POPs were statistically associated with lower birth weight (range, 98-170 g), whereas paternal concentrations of PBDEs (66, 99) were associated with higher birth weight. Differences in offspring head circumference, length, and ponderal index were also associated with parental exposures. CONCLUSIONS: Preconceptional maternal and paternal concentrations of several POPs were associated with statistically significant differences in birth size among offspring.			●	●			●			-		B	-
646	ヒト（生殖毒性）	Savitz, David A	Guest editorial: biomarkers of perfluorinated chemicals and birth weight	2007	Environ Health Perspect. 2007 Nov;115(11):A528-9. doi: 10.1289/ehp.10923.	No abstract available			●				●			-		C	-
647	ヒト（生殖毒性）	Starling, Anne P; Engel, Stephanie M; Whitworth, Kristina W; Richardson, David B; Stuebe, Alison M; Daniels, Julie L; Haug, Line Småstuen; Eggesbø, Merete; Becher, Georg; Sabaredzovic, Azemira; Thomsen, Cathrine; Wilson, Ralph E; Travlos, Gregory S; Hoppin, Jane A; Baird, Donna D; Longnecker, Matthew P	Perfluoroalkyl substances and lipid concentrations in plasma during pregnancy among women in the Norwegian Mother and Child Cohort Study	2014	Environ Int. 2014 Jan;62:104-12. doi: 10.1016/j.envint.2013.10.004. Epub 2013 Nov 2.	BACKGROUND: Perfluoroalkyl substances (PFASs) are widespread and persistent environmental pollutants. Previous studies, primarily among non-pregnant individuals, suggest positive associations between PFAS levels and certain blood lipids. If there is a causal link between PFAS concentrations and elevated lipids during pregnancy, this may suggest a mechanism by which PFAS exposure leads to certain adverse pregnancy outcomes, including preeclampsia. METHODS: This cross-sectional analysis included 891 pregnant women enrolled in the Norwegian Mother and Child (MoBa) Cohort Study in 2003-2004. Non-fasting plasma samples were obtained at mid-pregnancy and analyzed for nineteen PFASs. Total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein cholesterol, and triglycerides were measured in plasma. Linear regression was used to quantify associations between each PFAS exposure and each lipid outcome. A multiple PFAS model was also fitted. RESULTS: Seven PFASs were quantifiable in >50% of samples. Perfluorooctane sulfonate (PFOS) concentration was associated with total cholesterol, which increased 4.2mg/dL per inter-quartile shift (95% CI=0.8, 7.7) in adjusted models. Five of the seven PFASs studied were positively associated with HDL cholesterol, and all seven had elevated HDL associated with the highest quartile of exposure. Perfluoroundecanoic acid showed the strongest association with HDL: HDL increased 3.7 mg/dL per inter-quartile shift (95% CI=2.5, 4.9). CONCLUSION: Plasma concentrations of PFASs were positively associated with HDL cholesterol, and PFOS was positively associated with total cholesterol in this sample of pregnant Norwegian women. While elevated HDL is not an adverse outcome per se, elevated total cholesterol associated with PFASs during pregnancy could be of concern if causal. cholesterol in this sample of pregnant Norwegian women. While elevated HDL is not an adverse outcome per se, elevated total cholesterol associated with PFASs during pregnancy could be of concern if causal.			●	●			●			-		B	-
648	ヒト（生殖毒性）	Steenland, Kyle; Barry, Vaughn; Savitz, David	Serum perfluorooctanoic acid (PFOA) and birthweight: an updated meta analysis with bias analysis	2018	Epidemiology. 2018 Nov;29(6):765-776. doi: 10.1097/EDE.0000000000000903.	BACKGROUND: A recent meta-analysis of 15 studies found a change in birthweight of -12.8 g (95% CI = -23.1, -2.38) per ng/ml PFOA in maternal or cord blood and -27.1 g (-50.6, -3.6) per log ng/ml PFOA. Almost all studies were done in low-exposed populations. There are nine new studies, adding 6,019 births to the previous 6,937 births. METHODS: We conducted a meta-analysis of 24 studies. To combine all results, we approximated results for untransformed PFOA from nine studies using log-transformed PFOA. We also included another large study, excluded from previous analyses, in a sensitivity analysis. RESULTS: We found a change of birthweight of -10.5 g (-16.7, -4.4) for every ng/ml PFOA in maternal or cord blood. After adding one previously excluded large study, we found little evidence of an association (-1.0 g; 95% CI = -2.4, 0.4). Restricting to studies where blood was sampled from mothers early in the pregnancy or shortly before conception (5,393 births), we found little association of PFOA with birthweight (-3.3 g [-9.6, 3.0]). In studies where blood was sampled late in the pregnancy (7563 pregnancies), lower birthweight was associated with higher PFOA (-17.8 [-25.0, -10.6]). CONCLUSION: Present human evidence provides only modest support for decreased birthweight with increasing PFOA. Studies with a wide range of exposure, and studies with blood sampled early in pregnancy, showed little or no association of PFOA with birthweight. These are studies in which confounding and reverse causality would be of less concern.			●	●						-		B	-
649	ヒト（生殖毒性）	Verner, Marc-André; Loccisano, Anne E; Morken, Nils-Halvdan; Yoon, Miyoung; Wu, Huali; McDougall, Robin; Maisonet, Mildred; Marcus, Michele; Kishi, Reiko; Miyashita, Chihiro; Chen, Mei-Huei; Hsieh, Wu-Shiun; Andersen, Melvin E; Clewell, Harvey J 3rd; Longnecker, Matthew P	Associations of Perfluoroalkyl Substances (PFAS) with lower birth weight: an evaluation of potential confounding by glomerular filtration rate using a physiologically based pharmacokinetic model (PBPK)	2015	Environ Health Perspect. 2015 Dec;123(12):1317-24. doi: 10.1289/ehp.1408837. Epub 2015 May 22.	BACKGROUND: Prenatal exposure to perfluoroalkyl substances (PFAS) has been associated with lower birth weight in epidemiologic studies. This association could be attributable to glomerular filtration rate (GFR), which is related to PFAS concentration and birth weight. OBJECTIVES: We used a physiologically based pharmacokinetic (PBPK) model of pregnancy to assess how much of the PFAS-birth weight association observed in epidemiologic studies might be attributable to GFR. METHODS: We modified a PBPK model to reflect the association of GFR with birth weight (estimated from three studies of GFR and birth weight) and used it to simulate PFAS concentrations in maternal and cord plasma. The model was run 250,000 times, with variation in parameters, to simulate a population. Simulated data were analyzed to evaluate the association between PFAS levels and birth weight due to GFR. We compared simulated estimates with those from a meta-analysis of epidemiologic data. RESULTS: The reduction in birth weight for each 1-ng/mL increase in simulated cord plasma for perfluorooctane sulfonate (PFOS) was 2.72 g (95% CI: -3.40, -2.04), and for perfluorooctanoic acid (PFOA) was 7.13 g (95% CI: -8.46, -5.80); results based on maternal plasma at term were similar. Results were sensitive to variations in PFAS level distributions and the strength of the GFR-birth weight association. In comparison, our meta-analysis of epidemiologic studies suggested that each 1-ng/mL increase in prenatal PFOS and PFOA levels was associated with 5.00 g (95% CI: -21.66, -7.78) and 14.72 g (95% CI: -8.92, -1.09) reductions in birth weight, respectively. CONCLUSION: Results of our simulations suggest that a substantial proportion of the association between prenatal PFAS and birth weight may be attributable to confounding by GFR and that confounding by GFR may be more important in studies with sample collection later in pregnancy.			●	●			●			-	1	A	-
650	ヒト（生殖毒性）	Vestergaard, Sonja; Nielsen, Flemming; Andersson, Anne-Maria; Hjøllund, Niels Henrik; Grandjean, Philippe; Andersen, Helle Raun; Jensen, Tina Kold	Association between perfluorinated compounds and time to pregnancy in a prospective cohort of Danish couples attempting to conceive	2012	Hum Reprod. 2012 Mar;27(3):873-80. doi: 10.1093/humrep/der450. Epub 2012 Jan 13.	BACKGROUND: Perfluorinated chemicals (PFCs) have been widely used and have emerged as important food contaminants. A recent study on pregnant women suggested that PFC exposure was associated with a longer time to pregnancy (TTP). We examined the association between serum concentrations of PFCs in females and TTP in 222 Danish first-time pregnancy planners during the years 1992-1995. METHODS: The couples were enrolled in the study when discontinuing birth control and followed for six menstrual cycles or until a clinically recognized pregnancy occurred. Fecundability ratio (FR) was calculated using discrete-time survival models. In addition, odds ratio (OR) for TTP >6 cycles was calculated. RESULTS: OR for TTP >6 cycles for those with PFC concentrations above the median were 0.96 [95% confidence interval (CI): 0.54-1.64] for perfluorooctane sulfonic acid (PFOS), the major PFC, compared with those below the median. FRs for those with PFOS concentrations above the median were 1.05 (95% CI: 0.74-1.48) compared with those below the median. Other PFCs showed the same lack of association with TTP. The results were not affected by adjustment for covariates. PFOS and perfluorooctanoic acid concentrations were similar to those observed in a previous Danish study. CONCLUSIONS: These findings suggest that exposure to PFCs affects TTP only to a small extent, if at all.			●	●		●				-		B	-
651	ヒト（生殖毒性）	Vestergren, Robin; Ullah, Shahid; Cousins, Ian T; Berger, Urs	A matrix effect-free method for reliable quantification of perfluoroalkyl carboxylic acids and perfluoroalkane sulfonic acids at low parts per trillion levels in dietary samples	2012	J Chromatogr A. 2012 May 11;1237:64-71. doi: 10.1016/j.chroma.2012.03.023. Epub 2012 Mar 14.	In recent exposure modeling studies diet has been identified as the dominant pathway of human exposure to perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS). However, the paucity of highly sensitive and accurate analytical data to support these studies means that their conclusions are open to question. Here a novel matrix effect-free method is described for ultra-trace analysis of perfluoroalkyl carboxylic acids and perfluoroalkane sulfonic acids in dietary samples of varied composition. The method employs ion pair extraction of the analytes into methyl tert-butyl ether and subsequent solid phase extraction clean-up on Florisil and graphitized carbon. The target compounds are separated and detected using ultra performance liquid chromatography coupled to tandem mass spectrometry. Special care was taken to avoid procedural blank contamination and potential contamination sources were elucidated. The performance of the method was validated for five different food test matrices including a duplicate diet sample. Method detection limits in the low to sub pgg(-1) range were obtained for all target analytes, which is 5-100 times more sensitive than previously reported for duplicate diet samples. Total method recoveries were consistently between 50 and 80% for all analytes in all tested food matrices and effects of co-extracted matrix constituents on ionization of the target compounds were found to be negligible. The precision of the method (defined as percentage relative standard deviation) at concentrations close to the respective method limits of quantification was <15% for all analytes. Accurate quantification at ultra-trace levels was demonstrated by laboratory control spike experiments. For the first time the presence of long-chain PFCAs in duplicate diet samples is reported. The method presented here can thus support an improved assessment of human exposure from dietary intake for a range of PFCA and PFSA homologues. Re-analysis of duplicate diet samples, which had been analyzed earlier using another analytical methodology, indicated that dietary intake of PFOA and PFOS may previously have been overestimated.			●							-		C	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献ランク①	文献ランク②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
652	ヒト（発生毒性）	Andersen, Camilla Schou; Fei, Chunyuan; Gamborg, Michael; Nohr, Ellen Aagaard; Sørensen, Thorkild I A; Olsen, Jørn	Prenatal exposures to perfluorinated chemicals and anthropometric measures in infancy	2010	Am J Epidemiol. 2010 Dec 1;172(11):1230-7. doi: 10.1093/aje/kwq289. Epub 2010 Oct 12.	Perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) are persistent chemicals that may affect growth early in life. The authors estimated the associations between maternal plasma levels of PFOS and PFOA and infants' weight, length, and body mass index development during the first year of life. Fourteen hundred women were randomly selected from the Danish National Birth Cohort among those who provided blood samples early in pregnancy and gave birth to liveborn singletons between 1996 and 2002. Weight and length information at 5 and 12 months of age was available for 1,010 children. Multiple linear regression models were used for analyses, and maternal PFOS and PFOA concentrations (ng/mL) were inversely related to children's weight in the first year of life: adjusted regression coefficients: 0.8 g (95% confidence interval(CI): 4.2, 2.6) at 5 months and 5.8 g (95% CI:10.4, 1.2) at 12 months for perfluorooctanesulfonate(PFOS); 9.4 g (95% CI: 28.6, 9.9) at 5 months and 19.0 g (95% CI: 44.9, 6.8) at 12 months for perfluorooctanoate(PFOA) [corrected]. A similar pattern was observed for body mass index measurements, and no associations with length were found. After sex stratification, the inverse associations with weight and body mass index were more pronounced in boys, and no clear association was seen for girls.				●	●	●				-		B	-
653	ヒト（発生毒性）	Andersen, Camilla Schou; Fei, Chunyuan; Gamborg, Michael; Nohr, Ellen A; Sørensen, Thorkild I A; Olsen, Jørn	Prenatal exposures to perfluorinated chemicals and anthropometry at 7 years of age	2013	Am J Epidemiol. 2013 Sep 15;178(6):921-7. doi: 10.1093/aje/kwt057. Epub 2013 Jul 3.	Fetal exposure to the perfluoroalkyl acids, perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA), has been associated with lower birth weight and lower weight and body mass index (weight (kg)/height (m)(2)) in early infancy. It is, however, unclear if exposure to prenatal PFOS and PFOA has a lasting influence on growth. We estimated the associations between the maternal plasma level of PFOS or PFOA and the children's body mass index, waist circumference, and risk of overweight at 7 years of age. A total of 1,400 women were randomly selected from the Danish National Birth Cohort among those who provided blood samples early in pregnancy and gave birth to liveborn singletons in 1996-2002. Weight and height information at 7 years was available for 811 children. Multiple linear and logistic regression models were used for analyses. Maternal PFOS and PFOA concentrations were overall inversely but nonsignificantly associated with the children's body mass index, waist circumference, and risk of overweight at 7 years of age. In conclusion, plasma levels of PFOS and PFOA in pregnant women did not seem to have any appreciable influence on their children's anthropometry at this point in childhood.				●						-		B	-
654	ヒト（生殖毒性）	Bach, Cathrine Carlsen; Henriksen, Tine Brink; Bossi, Rossana; Bech, Bodil Hammer; Fuglsang, Jens; Olsen, Jørn; Nohr, Ellen Aagaard	Perfluoroalkyl acid concentrations in blood samples subjected to transportation and processing delay	2015	PLoS One. 2015 Sep 10;10(9):e0137768. doi: 10.1371/journal.pone.0137768. eCollection 2015.	BACKGROUND: In studies of perfluoroalkyl acids, the validity and comparability of measured concentrations may be affected by differences in the handling of biospecimens. We aimed to investigate whether measured plasma levels of perfluoroalkyl acids differed between blood samples subjected to delay and transportation prior to processing and samples with immediate processing and freezing. METHODS: Pregnant women recruited at Aarhus University Hospital, Denmark, (n = 88) provided paired blood samples. For each pair of samples, one was immediately processed and plasma was frozen, and the other was delayed and transported as whole blood before processing and freezing of plasma (similar to the Danish National Birth Cohort). We measured 12 perfluoroalkyl acids and present results for compounds with more than 50% of samples above the lower limit of quantification. RESULTS: For samples taken in the winter, relative differences between the paired samples ranged between -77 and +38% for individual perfluoroalkyl acids. In most cases concentrations were lower in the delayed and transported samples, e.g. the relative difference was -29% (95% confidence interval -30; -27) for perfluorooctane sulfonate. For perfluorooctanoate there was no difference between the two setups [corresponding estimate 1% (0, 3)]. Differences were negligible in the summer for all compounds. CONCLUSIONS: Transport of blood samples and processing delay, similar to conditions applied in some large, population-based studies, may affect measured perfluoroalkyl acid concentrations, mainly when outdoor temperatures are low. Attention to processing conditions is needed in studies of perfluoroalkyl acid exposure in humans.				●						-		B	-
655	ヒト（生殖毒性）	Bach CC, Liew Z, Bech BH, et al.	Additional file to perfluoroalkyl acids and time to pregnancy revisited: An update from the Danish National Birth Cohort [Environ Health 14:59]	2015	Environ Health. 2015 Jul 7;14:59. doi: 10.1186/s12940-015-0040-9.	No abstract available				●						既報への追加資料		D	-
656	ヒト（発生毒性）	Bae, Jisuk; Kim, Sungduk; Schisterman, Enrique F; Boyd Barr, Dana; Buck Louis, Germaine M	Maternal and paternal serum concentrations of perfluoroalkyl and polyfluoroalkyl substances and the secondary sex ratio	2015	Chemosphere. 2015 Aug;133:31-40. doi: 10.1016/j.chemosphere.2015.03.015. Epub 2015 Apr 2.	Select persistent environmental chemicals have been associated with a reduction in the secondary sex ratio (SSR), or the ratio of male to female live births. We evaluated preconception maternal, paternal, and couple serum concentrations of perfluoroalkyl and polyfluoroalkyl substances (PFASs) in relation to the SSR, given the absence of previous investigation. Two hundred thirty-three couples from Michigan and Texas were enrolled prior to conception and prospectively followed through delivery of a singleton birth, 2005-2009. Maternal and paternal serum concentrations (ng mL(-1)) were measured at baseline for seven PFASs. Logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for a male birth, after adjusting for potential confounders. When maternal and paternal PFAS concentrations were modeled jointly, five of the seven PFASs, including the two most prominent PFASs, perfluorooctane sulfonic acid and perfluorooctanoic acid, were not significantly associated with the SSR. However, paternal N-methyl-perfluorooctane sulfonamidoacetic acid (MeFOSAA) and perfluorononanoic acid (2nd versus 1st tertile, OR, 0.43, 95% CI, 0.21-0.88) were significantly associated with an excess of female births. Meanwhile, a dose-response relation was observed only for paternal MeFOSAA (2nd versus 1st tertile, OR, 0.53, 95% CI, 0.26-1.10; 3rd versus 1st tertile, OR, 0.34, 95% CI, 0.13-0.89). This study suggests a possible dose-response relation between a less prevalent PFAS and a reversal in the SSR, though the underlying mechanisms remain unknown and the findings await corroboration to eliminate other explanations including chance.				●						-		B	-
657	ヒト（内分泌系）	Barrett, Emily S; Chen, Chongshu; Thurston, Sally W; Haug, Line Småstuen; Sabaredzovic, Azemira; Fjeldheim, Frøydis Nyborg; Frydenberg, Hanne; Lipson, Susan F; Ellison, Peter T; Thune, Inger	Perfluoroalkyl substances and ovarian hormone concentrations in naturally cycling women	2015	Fertil Steril. 2015 May;103(5):1261-70.e3. doi: 10.1016/j.fertnstert.2015.02.001. Epub 2015 Mar 4.	OBJECTIVE: To examine associations between environmental exposure to perfluoroalkyl substances (PFASs) and ovarian hormone concentrations in naturally cycling women. DESIGN: E2 and P were measured in saliva samples collected daily for a single menstrual cycle and concentrations of PFASs (including perfluoroctane sulfonate [PFOS] and perfluoroctanoic acid) were measured in serum samples collected during the same cycle. SETTING: Not applicable. PATIENT(S): A total of 178 healthy, naturally cycling women, aged 25-35 years. INTERVENTION(S): None. MAIN OUTCOME MEASURE(S): Mean follicular E2 (cycle days -7 to -1, where 0 is the day of ovulation); mean luteal P (cycle days +2 to 10). RESULT(S): Among nulliparous, but not parous women, PFOS concentrations were inversely associated with E2 (β = -0.025, 95% CI -0.043, -0.007) and P (β = -0.027, 95% CI -0.048, -0.007). Similar, but weaker results were observed for perfluorooctanesulfonic acid. No associations were observed between other PFASs (including perfluoroctanoic acid) and ovarian steroid concentrations, nor were any associations noted in parous women. CONCLUSION(S): Our results demonstrate that PFOS and perfluorooctanesulfonic acid may be associated with decreased production of E2 and P in reproductive age women. These results suggest a possible mechanism by which PFASs affect women's health, and underscore the importance of parity in research on PFASs and women's reproductive health.				●						-	1	A	-
658	ヒト（発生毒性）	Barry, Vaughn; Darrow, Lyndsey A; Klein, Mitchel; Winquist, Andrea; Steenland, Kyle	Early life perfluorooctanoic acid (PFOA) exposure and overweight and obesity risk in adulthood in a community with elevated exposure	2014	Environ Res. 2014 Jul;132:62-9. doi: 10.1016/j.envres.2014.03.025. Epub 2014 Apr 16.	BACKGROUND: Infants and young children may be susceptible to developmental effects of perfluorooctanoic acid (PFOA) exposure. Two previous studies, one that examined a general population exposed to environmental PFOA levels and one conducted in mice exposed to experimental PFOA levels, found that early life exposure was associated with higher body mass index (BMI) in adulthood and effects may be stronger in women than in men. OBJECTIVES: Examine whether elevated early life PFOA exposure was associated with adult BMI among a group of mid-Ohio valley residents exposed to a wide range of early life PFOA levels due to emissions from a chemical plant. METHODS: The cohort consisted of 8764 adults aged 20-40 years who reported height and weight on a survey between 2008 and 2011. Annual retrospective early life PFOA serum concentrations were estimated for each participant based on residential history and nearby chemical plant emissions as well as background exposure not originating from the facility. We defined early life exposure as the estimated average PFOA serum concentration over the first three years of life. We examined the association between early life PFOA exposure and adult overweight (BMI ≥ 25 kg/m(2)) and obesity (BMI ≥ 30 kg/m(2)) risk using logistic and linear regression models. RESULTS: Nearly half the participants (45%) had early life PFOA exposure serum concentration estimates above background levels. Using participants who were exposed only to background PFOA levels as the referent category with quintiles of exposure above background, adjusted odds ratios (and 95% confidence intervals) for overweight risk by increasing exposure category for women were 1.0 (ref), 1.0 (0.8, 1.3), 1.0 (0.8, 1.2), 1.0 (0.8, 1.2), 0.9 (0.7, 1.1), and 0.9 (0.7, 1.1) and for men were 1.0 (ref), 0.9 (0.6, 1.1), 1.0 (0.7, 1.3), 1.0 (0.8, 1.4), 0.7 (0.5, 0.9), and 0.9 (0.7, 1.1). Odds ratios for adult obesity risk were similar. Regression coefficients from linear models using BMI as a continuous outcome showed no association between early life PFOA exposure and adult BMI. CONCLUSIONS: Elevated levels of PFOA exposure in early life were not associated with overweight and obesity risk in adulthood and results did not vary by sex.				●					●	-		C	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
659	ヒト（発生毒性）	Darrow LA, Howards PP, Winquist A, Steenland K.	PFOA and PFOS serum levels and miscarriage risk	2014	Epidemiology. 2014 Jul;25(4):505-12. doi: 10.1097/EDE.0000000000000103.	Background: Serum concentrations of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) were assessed in relation to miscarriage in a population of mid-Ohio River Valley residents highly exposed to PFOA through contaminated drinking water. Methods: Serum PFOA and PFOS concentrations were measured in 1129 women in 2005-2006 who reported pregnancy outcomes in follow-up interviews between 2008 and 2011. In the analysis, we included 1438 reported live births, stillbirths, and miscarriages with estimated conception dates after the serum measurements. Preconception serum levels of PFOA and PFOS were analyzed in relation to miscarriage using logistic regression and generalized estimating equations. Results: There was little evidence of association between PFOA and miscarriage. For PFOS, when including all reported prospective pregnancies, the odds ratio of miscarriage per log ng/ml increase was 1.21 (95% confidence interval = 0.94-1.55); in subanalyses restricted to each woman's first pregnancy conceived after the serum measurement, the odds ratio was 1.34 (1.02-1.76). Categorical analyses showed elevated odds ratios for the top 4 quintiles relative to the first quintile, without a monotonic trend. Positive associations between PFOS and miscarriage were strongest among nulligravid pregnancies. Conclusions: In this prospective study of miscarriage in a population exposed to high levels of PFOA and background levels of PFOS, we found little evidence of association with serum levels of PFOA and limited evidence of association with serum levels of PFOS.				●						-		B	-
660	ヒト（生殖毒性）	Dhingra, Radhika; Darrow, Lyndsey A; Klein, Mitch; Winquist, Andrea; Steenland, Kyle	Perfluorooctanoic acid exposure and natural menopause: A longitudinal study in a community cohort	2016	Environ Res. 2016 Apr;146:323-30. doi: 10.1016/j.envres.2015.12.037. Epub 2016 Jan 21.	INTRODUCTION: Perfluorooctanoic acid (PFOA), a suspected endocrine disruptor, is a bio-persistent chemical found at low levels in the serum of nearly all U.S. residents. Early menopause has been positively associated with serum PFOA in prior cross-sectional studies. METHODS: We conducted a longitudinal analysis of age at menopause among women, aged ≥40 years, (N=8759) in a Mid-Ohio Valley community cohort, exposed to high PFOA levels via contaminated drinking water. Using estimated retrospective year-specific serum PFOA concentrations (1951-2011), we examined the associations between PFOA, as cumulative exposure or year-specific serum estimates, and natural menopause using a Cox proportional hazards models. As participants were initially recruited in 2005-2006, we also analyzed the cohort prospectively (i.e., from the time of enrollment), using both modeled cumulative PFOA, and PFOA serum levels measured in 2005-2006. Women with hysterectomy (a competing risk) were either censored or excluded from the analysis. RESULTS: Neither in the retrospective nor the prospective cohort did we find a significant (at α=0.05) trend between PFOA exposure and natural menopause. The non-significant, hazard ratios by quintile of increasing cumulative serum PFOA were 1.00 (referent), 1.00, 1.09, 1.05 and 1.06 (trend test for log cumulative exposure: p=0.37) with hysterectomies censored, and 1.00 (referent), 1.06, 1.13, 1.09 and 1.11 (trend test for log cumulative exposure: p=0.85) with hysterectomies excluded. Year-specific serum estimates were also not associated with early menopause. CONCLUSION: Our data suggest that earlier age at menopause is not associated with PFOA exposure.		●		●						-		C	-
661	ヒト（発生毒性）	Donauer, Stephanie; Chen, Aimin; Xu, Yingying; Calafat, Antonia M; Sjodin, Andreas; Yolton, Kimberly	Prenatal exposure to polybrominated diphenyl ethers and polyfluoroalkyl chemicals and infant neurobehavior	2015	J Pediatr. 2015 Mar;166(3):736-42. doi: 10.1016/j.jpeds.2014.11.021. Epub 2014 Dec 16.	OBJECTIVE: To assess the impact of prenatal exposure to polybrominated diphenyl ethers (PBDEs) and polyfluoroalkyl chemicals (PFCs) on early infant neurobehavior. STUDY DESIGN: In a cohort of 349 mother/infant pairs, we measured maternal serum concentrations during pregnancy of PBDEs, including BDE-47 and other related congeners, as well as 2 common PFCs, perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid. When the infants were 5 weeks of age, we measured their neurobehavior by using the Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS). RESULTS: Neither PBDE nor PFC exposures during gestation were associated with the 11 individual NNNS outcomes included in our study; however, when we used latent profile analysis to categorize infants into neurobehavioral profiles based on performance on the NNNS (social/easygoing, high arousal/difficult, or hypotonic), a 10-fold increase in prenatal PFOA concentrations significantly increased the odds of being categorized as hypotonic compared with social/easygoing (aOR 3.79; 95% CI 1.1-12.8). CONCLUSIONS: Infants of mothers with greater serum concentrations of PFOA during pregnancy were more likely to be categorized as hypotonic. No association between PBDE concentrations and hypotonia was found. Additional studies should further investigate possible associations of prenatal PFC exposure and muscle tone in infants and children.				●						-		B	-
662	ヒト（発生毒性）	Fei, Chunyuan; McLaughlin, Joseph K; Tarone, Robert E; Olsen, Jørn	Fetal growth indicators and perfluorinated chemicals: A study in the Danish National Birth Cohort	2008	Am J Epidemiol. 2008 Jul 1;168(1):66-72. doi: 10.1093/aje/kwn095. Epub 2008 May 5.	Perfluorooctanoate (PFOA) and perfluorooctanesulfonate (PFOS) are widespread persistent organic pollutants that have been associated with reduced birth weight at doses expected in many pregnant populations. The authors randomly selected 1,400 pregnant women and their newborns from the Danish National Birth Cohort (1996-2002) to investigate whether these compounds reduce organ growth. PFOS and PFOA were measured in maternal blood samples taken early in pregnancy. Placental weight, birth length, and head and abdominal circumferences were measured shortly after birth by trained midwives or nurses. Maternal PFOA levels in early pregnancy were associated with smaller abdominal circumference and birth length. For each ng/ml increase in PFOA, birth length decreased by 0.069 cm (95% confidence interval: 0.024, 0.113) and abdominal circumference decreased by 0.059 cm (95% confidence interval: 0.012, 0.106). An inverse association was also observed between PFOA and placental weight and head circumference, and a positive association was observed with newborn ponderal index, but none of these associations was statistically significant. Maternal PFOS levels were not associated with any of the five fetal growth indicators. These findings suggest that fetal exposure to PFOA but not PFOS during organ development may affect the growth of organs and the skeleton.				●	●	●	●			-		B	-
663	ヒト（生殖毒性）	Fei, Chunyuan; Weinberg, Clarice R; Olsen, Jørn	Commentary: Perfluorinated chemicals and time to pregnancy: A link based on reverse causation?	2012	Epidemiology. 2012 Mar;23(2):264-6. doi: 10.1097/EDE.0b013e3182467608.	No abstract available				●					コメント		D	-
664	ヒト（発生毒性）	Høyer, Birgit Bjerre; Ramlau-Hansen, Cecilia Høst; Vrijheid, Martine; Valvi, Damaskini; Pedersen, Henning Sloth; Zviezdai, Valentyna; Jönsson, Bo A G; Lindh, Christian H; Bonde, Jens Peter; Toft, Gunnar	Anthropometry in 5- to 9-year-old Greenlandic and Ukrainian children in relation to prenatal exposure to perfluorinated alkyl substances	2015	Environ Health Perspect. 2015 Aug;123(8):841-6. doi: 10.1289/ehp.1408881. Epub 2015 Mar 26.	BACKGROUND: In some animal studies, perfluorinated alkyl substances are suggested to induce weight gain. Human epidemiological studies investigating these associations are sparse. OBJECTIVE: We examined pregnancy serum concentrations of perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) and the prevalence of offspring overweight (> 1 SD) and waist-to-height ratio (WHtR) > 0.5 at 5-9 years of age. METHODS: Sera from 1,022 pregnant women enrolled in the INUENDO cohort (2002-2004) from Greenland and Kharkiv (Ukraine) were analyzed for PFOA and PFOS using liquid chromatography-tandem mass spectrometry. Relative risks (RR) of being overweight and having WHtR > 0.5 in relation to continuous and categorized (tertiles) PFOA and PFOS were calculated at follow-up (2010-2012) using generalized linear models. RESULTS: Pooled PFOA median (range) was 1.3 (0.2-5.1) and PFOS median (range) was 10.8 (0.8-73.0) ng/mL. For each natural logarithm-unit (ln-unit) increase of pregnancy PFOA, the adjusted RR of offspring overweight was 1.11 [95% confidence interval (CI): 0.82, 1.53] in Greenlandic children. In Ukrainian children, the adjusted RR of offspring overweight was 1.02 (95% CI: 0.72, 1.44) for each ln-unit increase of pregnancy PFOA. Prenatal exposure to PFOS was not associated with overweight in country-specific or pooled analysis. The adjusted RR of having WHtR > 0.5 for each ln-unit increase of prenatal exposure to PFOA was 1.30 (95% CI: 0.97, 1.74) in the pooled analysis. For 1-ln-unit increase of prenatal exposure to PFOS, the adjusted RR of having a WHtR > 0.5 was 1.38 (95% CI: 1.05, 1.82) in the pooled analysis. CONCLUSIONS: The results indicate that prenatal PFOA and PFOS exposures may be associated with child waist-to-height ratio > 0.5. Prenatal PFOA and PFOS exposures were not associated with overweight.				●						-		B	-
665	ヒト（生殖毒性）	Knox, Sarah S; Jackson, Timothy; Frisbee, Stephanie J; Javins, Beth; Ducatman, Alan M	Perfluorocarbon exposure, gender and thyroid function in the C8 Health Project	2011	J Toxicol Sci. 2011 Aug;36(4):403-10. doi: 10.2131/jts.36.403.	Perfluorocarbons from common household products such as food containers, stain- resistant protection for clothing, furniture and carpets, paints, and fire-fighting foams are found in soil, water, plants, animal and human serum worldwide. Previous research has shown a significant association between these chemicals and thyroid disease in women. The present data from the C8 Health Project assessed thyroid function in a cross-sectional analysis of 52,296 adults with a year or more of exposure to perfluorooctanoate (PFOA) from drinking water. Outcomes were: thyroxine, T3 uptake, and thyroid stimulating hormone (TSH). Analyses were stratified by gender and age group (< 20 - < 50 years and > 50). Both PFOA and perfluorooctane sulfonate (PFOS) were associated with significant elevations in serum thyroxine and a significant reduction in T3 uptake in all participants. There were also significant gender/PFOS interactions for T3( )uptake and thyroxine, as well as gender/PFOA interactions for T3 uptake. Results provide evidence for disruption of thyroid function related to these common chemicals and possible mechanisms are discussed.				●	●	●				-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ラン①クン	文献ラン②クン
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
666	ヒト（発生毒性）	Lam, Juleen; Koustas, Erica; Sutton, Patrice; Johnson, Paula I; Atchley, Dylan S; Sen, Saunak; Robinson, Karen A; Axelrad, Daniel A; Woodruff, Tracey J	The Navigation Guide - evidence-based medicine meets environmental health: Integration of animal and human evidence for PFOA effects on fetal growth	2014	Environ Health Perspect. 2014 Oct;122(10):1040-51. doi: 10.1289/ehp.1307923. Epub 2014 Jun 25.	BACKGROUND: The Navigation Guide is a novel systematic review method to synthesize scientific evidence and reach strength of evidence conclusions for environmental health decision making. OBJECTIVE: Our aim was to integrate scientific findings from human and nonhuman studies to determine the overall strength of evidence for the question "Does developmental exposure to perfluorooctanoic acid (PFOA) affect fetal growth in humans?" METHODS: We developed and applied prespecified criteria to systematically and transparently a) rate the quality of the scientific evidence as "high," "moderate," or "low"; b) rate the strength of the human and nonhuman evidence separately as "sufficient," "limited," "moderate," or "evidence of lack of toxicity"; and c) integrate the strength of the human and nonhuman evidence ratings into a strength of the evidence conclusion. RESULTS: We identified 18 epidemiology studies and 21 animal toxicology studies relevant to our study question. We rated both the human and nonhuman mammalian evidence as "moderate" quality and "sufficient" strength. Integration of these evidence ratings produced a final strength of evidence rating in which review authors concluded that PFOA is "known to be toxic" to human reproduction and development based on sufficient evidence of decreased fetal growth in both human and nonhuman mammalian species. CONCLUSION: We concluded that developmental exposure to PFOA adversely affects human health based on sufficient evidence of decreased fetal growth in both human and nonhuman mammalian species. The results of this case study demonstrate the application of a systematic and transparent methodology, via the Navigation Guide, for reaching strength of evidence conclusions in environmental health.				●						-		B	-
667	ヒト（発生毒性）	Nolan, Lynda A; Nolan, John M; Shofer, Frances S; Rodway, Nancy V; Emmett, Edward A	The relationship between birth weight, gestational age and perfluorooctanoic acid (PFOA)-contaminated public drinking water	2009	Reprod Toxicol. 2009 Jun;27(3-4):231-238. doi: 10.1016/j.reprotox.2008.11.001. Epub 2008 Nov 13.	BACKGROUND: Recent studies have examined the associations between perfluorooctanoic acid (PFOA) levels in cord blood and maternal plasma with lowered birth weight and gestational age in humans; however, no study has examined these effects in a population of known high PFOA exposure. Residents drinking PFOA-contaminated water from the Little Hocking Water Association (LHWA) in Washington County, Ohio have serum PFOA levels approximately 80 times those in the general U.S. population. OBJECTIVES: To compare birth weights and gestational ages of neonates born to mothers residing in zip codes with water service provided completely, partially or not at all by the LHWA. METHODS: Multiple logistic and linear regression analyses were performed on singleton neonatal birth weight data supplied by the Ohio Department of Health to examine the associations between LHWA water service category (used as a surrogate for PFOA exposure) with mean birth weight, mean gestational age, the likelihood of low birth weight (<2500 g), and the likelihood of preterm birth (<37 completed weeks of gestation). All models were adjusted for maternal age, gestational age, sex, race and population-level socioeconomic status. RESULTS: The incidence of low birth weight, preterm birth, mean birth weight and mean gestational age of neonates did not significantly differ among water service categories. CONCLUSION: Markedly elevated PFOA exposure, as categorized by water service category, is not associated with increased risk of lowered birth weight or gestational age. This study does not confirm earlier findings of an association between PFOA and lowered birth weight observed at normal population levels.				●		●	●			-		C	-
668	ヒト（発生毒性）	Nolan, Lynda A; Nolan, John M; Shofer, Frances S; Rodway, Nancy V; Emmett, Edward A	Congenital anomalies, labor/delivery complications, maternal risk factors and their relationship with perfluorooctanoic acid (PFOA)-contaminated public drinking water	2010	Reprod Toxicol. 2010 Apr;29(2):147-55. doi: 10.1016/j.reprotox.2009.10.012. Epub 2009 Nov 6.	BACKGROUND: We have previously examined the associations between perfluorooctanoic acid (PFOA) exposure, birth weight and gestational age in individuals exposed to PFOA-contaminated residential drinking water from the Little Hocking Water Association (LHWA). In this investigation, we expand the scope of our analysis to examine the associations between PFOA, congenital anomalies, labor and delivery complications and maternal risk factors. OBJECTIVES: To compare the likelihood of congenital anomalies, labor and delivery complications and maternal risk factors in neonates and their mothers residing in zip codes with public water service provided completely, partially or not at all by the LHWA. METHODS: Logistic regression analyses were performed on singleton neonatal birth outcome data supplied by the Ohio Department of Health to examine the associations between LHWA water service category and the outcomes of interest. When possible, models were adjusted for maternal age, preterm birth, neonatal sex, race, maternal education, alcohol use, tobacco use and diabetic status. RESULTS: Increased PFOA exposure, as assessed by water service category, was not associated with an overall increase in the likelihood of congenital anomalies or any specific diagnosis (adjusted OR: 1.4, 95% CI: 0.34-3.3). The overall likelihood of labor and delivery complications was significantly lower among mothers with water service provided by the LHWA, as compared to mothers not serviced by the LHWA (adjusted OR: 0.65, 95% CI: 0.46-0.92). A significant increase in the likelihood of anemia (crude OR: 11, 95% CI: 1.8-64) and dysfunctional labor (crude OR: 5.3, 95% CI: 1.2-24) was noted for mothers residing within zip codes serviced by the LHWA, but the number of reported cases was very small. CONCLUSION: At the levels measured in the LHWA, we conclude that PFOA is not associated with increased risk of congenital anomalies, most labor and delivery complications and maternal risk factors. Additional research is required to assess the observed associations between PFOA, anemia and dysfunctional labor.				●		●				-		C	-
669	ヒト（生殖毒性）	Raymer, James H; Michael, Larry C; Studabaker, William B; Olsen, Geary W; Sloan, Carol S; Wilcosky, Timothy; Walmer, David K	Concentrations of perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) and their associations with human semen quality measurements	2012	Reprod Toxicol. 2012 Jul;33(4):419-427. doi: 10.1016/j.reprotox.2011.05.024. Epub 2011 Jun 29.	A total of 256 men were studied to evaluate whether serum concentrations of perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) impacted semen quality or reproductive hormones. Blood and semen were collected and analyzed for perfluorochemicals and reproductive and thyroid hormones. Semen quality was assessed using standard clinical methods. Linear and logistic modeling was performed with semen profile measurements as outcomes and PFOS and PFOA in semen and plasma as explanatory variables. Adjusting for age, abstinence, and tobacco use, there was no indication that PFOA or PFOS was significantly associated with volume, sperm concentration, percent motility, swim-up motility and concentration, and directional motility (a function of motility and modal progression). Follicle-stimulating hormone was not associated with either PFOA or PFOS. Luteinizing hormone was positively correlated with plasma PFOA and PFOS, but not semen PFOS. Important methodological concerns included the lack of multiple hormonal measurements necessary to address circadian rhythms.				●	●	●			●	-		B	-
670	ヒト（生殖毒性）	Specht, Ina Olmer; Hougaard, Karin S; Spanò, Marcello; Bizzaro, Davide; Manicardi, Gian Carlo; Lindh, Christian H; Toft, Gunnar; Jönsson, Bo A G; Giwercman, Aleksander; Bonde, Jens Peter E	Sperm DNA integrity in relation to exposure to environmental perfluoroalkyl substances	2012	Reprod Toxicol. 2012 Jul;33(4):577-583. doi: 10.1016/j.reprotox.2012.02.008. Epub 2012 Mar 15.	Perfluoroalkyl substances (PFASs) can interfere with male reproductive function, but evidence in humans is limited. Six hundred four fertile men (199 from Greenland, 197 from Poland and 208 from Ukraine) were enrolled in the study. We measured four PFASs in serum (PFOS, PFOA, PFNA and PFHxS) and concurrent DNA damage in spermatozoa by sperm chromatin structure assay (SCSA) and in situ terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) assay, apoptotic markers in semen (Fas-receptor and Bcl-xL), and reproductive hormones in serum. No association between PFASs and SCSA, apoptotic markers or reproductive hormones emerged. We observed a slight increase in SHBG and TUNEL-positivity with increased PFOA exposure in men from Greenland. Thus, consistent evidence that PFAS exposure interferes with sperm DNA fragmentation, apoptosis or reproductive hormones was not found.				●					●	-		B	-
671	ヒト（発生毒性）	Stein, Cheryl R; Savitz, David A; Elston, Beth; Thorpe, Phoebe G; Gilboa, Suzanne M	Perfluorooctanoate exposure and major birth defects	2014	Reprod Toxicol. 2014 Aug;47:15-20. doi: 10.1016/j.reprotox.2014.04.006. Epub 2014 May 4.	Perfluorooctanoate (PFOA) is detectable in umbilical cord blood and amniotic fluid. Some toxicological findings suggest that perfluoroalkyl substances may be teratogenic. Using data from the C8 Health Project, a 2005-2006 survey in a Mid-Ohio Valley community exposed to PFOA through contaminated drinking water, we examined the association between estimated prenatal PFOA concentration and maternally reported birth defects (n=325) among 10,262 live singleton or multiple births from 1990 to 2006. Logistic regression models accounted for siblings using generalized estimating equations. There was generally no association between estimated PFOA concentration and birth defects, with the possible exception of brain defects, where the odds ratio adjusted for year of conception was 2.6 (95% confidence interval 1.3-5.1) for an increase in estimated PFOA exposure from the 25th to 75th percentile. This estimate, however, was based on 13 cases and may represent a chance finding. Further investigation of this potential association may be warranted.				●						-		B	-
672	ヒト（代謝）	Timmermann, Clara Amalie G; Rossing, Laura I; Grøntved, Anders; Ried-Larsen, Mathias; Dalgård, Christine; Andersen, Lars B; Grandjean, Philippe; Nielsen, Flemming; Svendsen, Kira D; Scheike, Thomas; Jensen, Tina K	Adiposity and glycemic control in children exposed to perfluorinated compounds	2014	J Clin Endocrinol Metab. 2014 Apr;99(4):E608-14. doi: 10.1210/jc.2013-3460. Epub 2014 Feb 25.	OBJECTIVE: Our objective was to explore whether childhood exposure to perfluorinated and polyfluorinated compounds (PFCs), widely used stain- and grease-repellent chemicals, is associated with adiposity and markers of glycemic control. MATERIALS AND METHODS: Body mass index, skinfold thickness, waist circumference, leptin, adiponectin, insulin, glucose, and triglyceride concentrations were assessed in 8- to 10-year-old children in 1997 in a subset of the European Youth Heart Study, Danish component. Plasma PFC concentrations were available from 499 children. Linear regression models were performed to determine the association between PFC exposure and indicators of adiposity and markers of glycemic control. RESULTS: There was no association between PFC exposures and adiposity or markers of glycemic control in normal-weight children. Among overweight children, an increase of 10 ng perfluorooctane sulfonic acid/mL plasma was associated with 16.2% (95% confidence interval [CI], 5.2%-28.3%) higher insulin concentration, 12.0% (95% CI, 2.4%-22.4%) higher β-cell activity, 17.6% (95% CI, 5.8%-30.8%) higher insulin resistance, and 8.6% (95% CI, 1.2%-16.5%) higher triglyceride concentrations, and an increase of 10 ng perfluorooctanoic acid/mL plasma was associated with 71.6% (95% CI, 2.4%-187.5%) higher insulin concentration, 67.5% (95% CI, 5.5%-166.0%) higher β-cell function, 73.9% (95% CI, 0.2%-202.0%) higher insulin resistance, and 76.2% (95% CI, 22.8%-153.0%) higher triglyceride concentrations. DISCUSSION: Increased PFC exposure in overweight 8- to 10-year-old children was associated with higher insulin and triglyceride concentrations. Chance findings may explain some of our results, and due to the cross-sectional design, reverse causation cannot be excluded. The findings therefore need to be confirmed in longitudinal studies.				●						-	1	A	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	情報抽出	文献ツール①	文献ツール②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022					
673	ヒト（発生毒性）	Washino, Noriaki; Saijo, Yasuaki; Sasaki, Seiko; Kato, Shizue; Ban, Susumu; Konishi, Kanae; Ito, Rie; Nakata, Ayako; Iwasaki, Yusuke; Saito, Koichi; Nakazawa, Hiroyuki; Kishi, Reiko	Correlations between prenatal exposure to perfluorinated chemicals and reduced fetal growth	2009	Environ Health Perspect. 2009 Apr;117(4):660-7. doi: 10.1289/ehp.11681. Epub 2008 Nov 4.	BACKGROUND: Perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) are man-made, ubiquitous, and persistent contaminants in the environment, wildlife, and humans. Although recent studies have shown that these chemicals interfere with fetal growth in humans, the results are inconsistent. OBJECTIVES: Our goal was to investigate the correlation between relatively low levels of PFOS and PFOA in maternal serum and birth weight and birth size. METHODS: We conducted a hospital-based prospective cohort study between July 2002 and October 2005 in Sapporo, Japan. A total of 428 women and their infants were involved in the study. We obtained characteristics of the mothers and infants from self-administered questionnaire surveys and from medical records. We analyzed maternal serum samples for PFOS and PFOA by liquid chromatography-tandem mass spectrometry (LC/MS/MS). RESULTS: After adjusting for confounding factors, PFOS levels negatively correlated with birth weight [per log10 unit: beta = -148.8 g; 95% confidence interval (CI), -297.0 to -0.5 g]. In addition, analyses stratified by sex revealed that PFOS levels negatively correlated with birth weight only in female infants (per log10 unit: beta = -269.4 g; 95% CI, -465.7 to -73.0 g). However, we observed no correlation between PFOA levels and birth weight. CONCLUSION: Our results indicate that in utero exposure to relatively low levels of PFOS was negatively correlated with birth weight.				●			●			-			B	-
674	ヒト（発生毒性）	Whitworth, Kristina W; Haug, Line S; Baird, Donna D; Becher, Georg; Hoppin, Jane A; Skjaerven, Rolv; Thomsen, Cathrine; Eggesbo, Merete; Travlos, Gregory; Wilson, Ralph; Cupul-Uicab, Lea A; Brantsaeter, Anne Lise; Longnecker, Matthew P	Perfluorinated compounds in relation to birth weight in the Norwegian Mother and Child Cohort Study	2012	Am J Epidemiol. 2012 Jun 15;175(12):1209-16. doi: 10.1093/aje/kwr459. Epub 2012 Apr 19.	Perfluorooctane sulfonate and perfluorooctanoic acid are perfluorinated compounds (PFCs) widely distributed in the environment. Previous studies of PFCs and birth weight are equivocal. The authors examined this association in the Norwegian Mother and Child Cohort Study (MoBa), using data from 901 women enrolled from 2003 to 2004 and selected for a prior case-based study of PFCs and subfecundity. Maternal plasma samples were obtained around 17 weeks of gestation. Outcomes included birth weight z scores, preterm birth, small for gestational age, and large for gestational age. The adjusted birth weight z scores were slightly lower among infants born to mothers in the highest quartiles of PFCs compared with infants born to mothers in the lowest quartiles: for perfluorooctane sulfonate, β = -0.18 (95% confidence interval: -0.41, 0.05) and, for perfluorooctanoic acid, β = -0.21 (95% confidence interval: -0.45, 0.04). No clear evidence of an association with small for gestational age or large for gestational age was observed. Perfluorooctane sulfonate and perfluorooctanoic acid were each associated with decreased adjusted odds of preterm birth, although the cell counts were small. Whether some of the associations suggested by these findings may be due to a noncausal pharmacokinetic mechanism remains unclear.				●			●	●		-			B	-
675	ヒト（生殖毒性）	Whitworth, Kristina W; Haug, Line S; Sabaredzovic, Azemira; Eggesbo, Merete; Longnecker, Matthew P	Brief report: Plasma concentrations of perfluorooctane sulfonamide and time-to-pregnancy among primiparous women	2016	Epidemiology. 2016 Sep;27(5):712-5. doi: 10.1097/EDE.0000000000000524.	BACKGROUND: A previous study reported a negative association between perfluorooctane sulfonamide (PFOSA) concentrations and fecundability. METHODS: We examined this association among women enrolled in the Norwegian Mother and Child Cohort Study (MoBa), in 2003-2004. This analysis was restricted to 451 primiparous women to avoid bias due to previous pregnancy. Self-reported time-to-pregnancy (TTP) and plasma were obtained around 18 weeks of gestation. Approximately half of the women had measurable PFOSA levels; missing values were multiply imputed. We used the logistic analogue of discrete-time survival analysis to examine the adjusted association between PFOSA, other perfluoroalkyl substances, and TTP. RESULTS: The median-measured PFOSA concentration was 0.03 ng/ml (interquartile range = 0.02, 0.07). The age and body mass index-adjusted association between an interquartile distance increase in PFOSA and TTP was 0.91 (95% confidence interval = 0.71, 1.17). Imputation of missing PFOSA resulted in similar estimates. No association was observed with other perfluoroalkyl substances. CONCLUSION: Based on a weakly decreased fecundability odds ratio, we found only limited support for an association between plasma PFOSA concentrations and TTP among primiparous women.				●						-			C	-
676	ヒト（生殖発生毒性）	Chen, G; Xu, LL; Huang, YF; Wang, Q; Wang, BH; Yu, ZH; Shi, QM; Hong, JW; Li, J; Xu, LC.	Prenatal exposure to perfluorooctane sulfonate impairs placental angiogenesis and induces aberrant expression of LncRNA Xist	2018	Biomed Environ Sci. 2018 Nov;31(11):843-847. doi: 10.3967/bes2018.111.	No abstract available		●							-			C	-
677	ヒト（生殖発生毒性）	Chen, MH; Ng, S; Hsieh, CJ; Lin, CC; Hsieh, WS; Chen, PC.	The impact of prenatal perfluoroalkyl substances exposure on neonatal and child growth	2017	Sci Total Environ. 2017 Dec 31;607-608:669-675. doi: 10.1016/j.scitotenv.2017.06.273. Epub 2017 Jul 27.	BACKGROUNDPerfluoroalkyl substances (PFASs) are wildly distributed environmental pollutants. Laboratory mice exposed prenatally to PFASs develop smaller birth weight but are more likely to become obese in adulthood. The evidences in human studies are still inconclusive.METHODSThe participants were 429 mother-infant pairs from Taiwan Birth Panel Study. These children were followed serially and growth data were collected through face to face interviews and records in Child Healthcare Handbooks until 108months of age. The age-specific z-scores for weight (WAZ), length/height (LAZ/HAZ) and BMI (BMIAZ) were calculated. PFASs in umbilical cord blood were analyzed by ultra-high-performance liquid chromatography/tandem mass spectrometry.RESULTSAt birth, perfluorooctyl sulfonate (PFOS) levels were negatively associated with weight and height [per ln unit: adjusted β (95% confidence interval, CI)=-0.14 (-0.26, -0.01) for WAZ and -0.16 (-0.31, -0.02) for LAZ]. However, these adverse impacts diminished as children grow up. When stratified the analysis by gender, the effects of prenatal PFOS exposure were more obvious for girls especially during the time span of 6 to 12 and 12 to 24months of age [per ln unit: adjusted β (95% CI)=-0.25 (-0.47, -0.04) and -0.24 (-0.41, -0.04) for WAZ, respectively; per ln unit: adjusted β (95% CI)=-0.33 (-0.59, -0.08) and -0.25 (-0.45, -0.05) for BMIAZ, respectively}. Later in the period of 60 to 108months of age, positive association between prenatal PFOS exposure and girls' BMI was observed [per ln unit: adjusted β (95% CI)=0.34 (0.007, 0.68) for BMIAZ]. There was little evidence in these data for a consistent association of perfluorooctanoic acid (PFOA) with any of the indicators.CONCLUSIONSOur study had shown that higher prenatal PFOS exposure was associated with decreased fetal growth, but the effects were diminished as children grow up. Modest effect of gender specific manner was observed.	●	●								-			B	-
678	ヒト（発生毒性）	Martin, JA; Hamilton, BE; Osterman, MJ; Driscoll, AK; Mathews, TJ.	Births: Final data for 2017	2018	Natl Vital Stat Rep. 2018 Nov;67(8):1-50.	Objectives-This report presents 2017 data on U.S. births according to a wide variety of characteristics. Trends in fertility patterns and maternal and infant characteristics are described and interpreted. Methods-Descriptive tabulations of data reported on the birth certificates of the 3.86 million births that occurred in 2017 are presented. Data are presented for maternal age, livebirth order, race and Hispanic origin, marital status, tobacco use, prenatal care, source of payment for the delivery, method of delivery, gestational age, birthweight, and plurality. Selected data by mother's state of residence and birth rates by age also are shown. Trend data for 2010 to 2017 are presented for selected items. Trend data by race and Hispanic origin are shown for 2016 and 2017. Results- A total of 3,855,500 births were registered in the United States in 2017, down 2% from 2016. Compared with rates in 2016, the general fertility rate declined to 60.3 births per 1,000 women aged 15-44. The birth rate for females aged 15-19 fell 7% in 2017. Birth rates declined for women in their 20s and 30s but increased for women in their early 40s. The total fertility rate declined to 1,765.5 births per 1,000 women in 2017. Birth rates for both married and unmarried women declined from 2016 to 2017. The percentage of women who began prenatal care in the first trimester of pregnancy rose to 77.3% in 2017; the percentage of all women who smoked during pregnancy declined to 6.9%. The cesarean delivery rate increased to 32.0% following 4 years of declines. Medicaid was the source of payment for 43.0% of all births in 2017, up 1% from 2016. The preterm birth rate rose for the third straight year, as did the rate of low birthweight. Twin and triplet and higher-order multiple birth rates were essentially stable in 2017.		●								-			D	-
679	ヒト（周産期影響）	Reyes, L; Mañalich, R.	Long-term consequences of low birth weight [Review]	2005	Kidney Int Suppl. 2005 Aug;(97):S107-11. doi: 10.1111/j.1523-1755.2005.09718.x.	There is accumulating evidence of the impact of low birth weight in adult age. Thus, the Barker theory and Brenner hypothesis gain more power. This article reviews and analyzes the evidence that supports the intrauterine origin of chronic noncommunicable diseases in adult age, particularly systemic arterial hypertension and chronic renal insufficiency. These are possibly related to lower nephron numbers, acquired in utero or later in life, which can increase susceptibility to kidney damage from diseases such as hypertension and diabetes mellitus, or cause arterial hypertension and secondary renal damage.		●								-			D	-
680	ヒト（発生毒性）	Fei, C., McLaughlin, J.K., Tarone, R.E. and Olsen, J.	Perfluorinated chemicals and fetal growth: a study within the Danish National Birth Cohort	2007	Environ Health Perspect. 2007 Nov;115(11):1677-82. doi: 10.1289/ehp.10506.	Background Perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) are man-made, persistent organic pollutants widely spread throughout the environment and human populations. They have been found to interfere with fetal growth in some animal models, but whether a similar effect is seen in humans is uncertain. Objectives We investigated the association between plasma levels of PFOS and PFOA in pregnant women and their infants' birth weight and length of gestation. Methods We randomly selected 1,400 women and their infants from the Danish National Birth Cohort among those who completed all four computer-assisted telephone interviews, provided the first blood samples between gestational weeks 4 and 14, and who gave birth to a single live-born child without congenital malformation. PFOS and PFOA were measured by high performance liquid chromatography–tandem mass spectrometer. Results PFOS and PFOA levels in maternal plasma were on average 35.3 and 5.6 ng/mL, respectively. Only PFOA levels were inversely associated with birth weight (adjusted β = − 10.63 g; 95% confidence interval, −20.79 to −0.47 g). Neither maternal PFOS nor PFOA levels were consistently associated with the risk for preterm birth or low birth weight. We observed no adverse effects for maternal PFOS or PFOA levels on small for gestational age. Conclusion Our nationwide cohort data suggest an inverse association between maternal plasma PFOA levels and birth weight. Because of widespread exposure to these chemicals, our findings may be of potential public health concern.					●	●		●		-			B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
681	ヒト（発生毒性）	La Rocca, Cinzia; Alessi, Eva; Bergamasco, Bruno; Caserta, Donatella; Ciardo, Francesca; Fanello, Emiliano; Focardi, Silvano; Guerranti, Cristiana; Stecca, Laura; Moscarini, Massimo; Perra, Guido; Tait, Sabrina; Zaghi, Carlo; Mantovani, Alberto	Exposure and effective dose biomarkers for perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) in infertile subjects: preliminary results of the PREVIENI project	2012	Int J Hyg Environ Health. 2012 Feb;215(2):206-11. doi: 10.1016/j.ijheh.2011.10.016. Epub 2011 Dec 23.	Perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) have been used as surfactants in various industry and consumer products. PFOS/PFOA are very persistent in the environment and bioaccumulate in humans. They are potential reproductive and developmental toxicants and are considered to be emerging endocrine disrupters (EDs). The Italian project PREVIENI, funded by the Italian Environment Ministry, aims to link environment and human health through the investigation of selected endocrine disrupters (EDs) exposure and associated biomarkers related to human infertility conditions. In the early PREVIENI phase, PFOS and PFOA were determined in 53 couples affected by an infertility status, enrolled in a metropolitan area, according to established inclusion criteria and informed consensus. Nuclear receptors related to chemical compounds interactions were selected as biomarkers of effect and their gene expression modulations were analyzed in human peripheral blood mononuclear cell (PBMC). Among couples, subjects not presenting infertility factors (IF--) were separated from affected subjects (IF++). Most IF-- serum samples showed PFOS and PFOA concentrations overlapping the limit of detection (LOD) of 0.5 ng/g wet weight (ww). A substantial percentage of IF++ serum samples showed PFOS concentrations >20-fold the LOD, i.e. from 3 to 50 ng/g ww. In male (50%, n=26) and from 3 to 144 ng/g ww in female (37%, n=30) samples. PFOA values were below the LOD levels in 90% of the total samples. Peroxisome proliferator-activated receptor-gamma (PPARγ) and aryl hydrocarbon receptor (AhR) showed a low level of expression in PBMC of both IF++ and IF-- groups. Whereas alpha and beta estrogen receptors (ERα and ERβ), androgen receptor (AR), and pregnane X receptor (PXR) were all upregulated in IF++ of both sexes with respect to IF-- group. Our preliminary results related to the metropolitan area indicate that subjects affected by infertility factors tend to have both higher PFOS levels and higher gene expression of specific nuclear receptors.					●						-		B	-
682	ヒト（発生毒性）	Bach, Cathrine Carlsen; Bech, Bodil Hammer; Brix, Nis; Nohr, Ellen Aagaard; Bonde, Jens Peter Ellekilde; Henriksen, Tine Brink	Perfluoroalkyl and polyfluoroalkyl substances and human fetal growth: a systematic review	2015	Crit Rev Toxicol. 2015 Jan;45(1):53-67. doi: 10.3109/10408444.2014.952400. Epub 2014 Nov 5.	BACKGROUND: Exposure to perfluoroalkyl and polyfluoroalkyl substances (PFASs) is ubiquitous in most regions of the world. The most commonly studied PFASs are perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA). Animal studies indicate that maternal PFAS exposure is associated with reduced fetal growth. However, the results of human studies are inconsistent. OBJECTIVES: To summarize the evidence of an association between exposure to PFASs, particularly PFOS and PFOA, and human fetal growth. METHODS: Systematic literature searches were performed in MEDLINE and EMBASE. We included original studies on pregnant women with measurements of PFOA or PFOS in maternal blood during pregnancy or the umbilical cord and associations with birth weight or related outcomes according to the PFAS level. Citations and references from the included articles were investigated to locate more relevant articles. Study characteristics and results were extracted to structured tables. The completeness of reporting as well as the risk of bias and confounding were assessed. RESULTS: Fourteen studies were eligible. In utero PFOA exposure was associated with decreased measures of continuous birth weight in all studies, even though the magnitude of the association differed and many results were statistically insignificant. PFOS exposure and birth weight were associated in some studies, while others found no association. CONCLUSIONS: Higher PFOS and PFOA concentrations were associated with decreased average birth weight in most studies, but only some results were statistically significant. The impact on public health is unclear, but the global exposure to PFASs warrants further investigation.						●	●			レビュー		A	-
683	ヒト（生殖毒性）	C8 Science Panel	C8 probable link reports (probable link evaluations for birth defects, pregnancy-induced hypertension and preeclampsia, miscarriage and stillbirths, preterm birth and low birth weight	2011	Available at: www.c8sciencepanel.org/prob_link.html.	No abstract available						●			C8 science panel ウェブサイト公表資料。対象外とする		B	-
684	ヒト（発生毒性）	Wendee Holtcamp	Obesogens: an environmental link to obesity	2012	Environ Health Perspect. 2012 Feb;120(2):a62-8. doi: 10.1289/ehp.120-a62.	No abstract available					●				-		C	-
685	ヒト（発生毒性）	Dobbins, Timothy A; Sullivan, Elizabeth A; Roberts, Christine L; Simpson, Judy M	Australian national birthweight percentiles by sex and gestational age, 1998–2007	2012	Med J Aust. 2012 Sep 3;197(5):291-4. doi: 10.5694/mja11.11331.	OBJECTIVE: To present updated national birthweight percentiles by gestational age for male and female singleton infants born in Australia. DESIGN AND SETTING: Cross-sectional population-based study of 2.53 million singleton live births in Australia between 1998 and 2007. MAIN OUTCOME MEASURES: Birthweight percentiles by gestational age and sex. RESULTS: Between 1998 and 2007, women in Australia gave birth to 2 539 237 live singleton infants. Of these, 2 537 627 had a gestational age between 20 and 44 weeks, and sex and birthweight data were available. Birthweight percentiles are presented by sex and gestational age for a total of 2 528 641 births, after excluding 8986 infants with outlying birthweights. Since the publication of the previous Australian birthweight percentiles in 1999, median birthweight for term babies has increased between 0 and 25 g for boys and between 5 g and 45 g for girls. CONCLUSIONS: There has been only a small increase in birthweight percentiles for babies of both sexes and most gestational ages since 1991-1994. These national percentiles provide a current Australian reference for clinicians and researchers assessing weight at birth.							●			-		D	-
686	ヒト（発生毒性）	Hall J, Case A, O'Neil L.	Northern Territory Midwives' Collection. Mothers and Babies 2013.	2015	Available online at https://digitallibrary.health.nt.gov.au/prodjspui/bitstream/10137/640/1/Northern%20Territory%20Midwives%20Collection%20Mothers%20and%20Babies%20Report%202013.pdf	This report summarises data from the 2013 Northern Territory (NT) Midwives' Collection. It includes population characteristics of mothers, maternal health status, antenatal information, conditions and procedures used in labour and childbirth, as well as birth outcomes of all births that occurred in 2013. While the NT Midwives' Collection contains information on both NT residents and non-NT residents who gave birth in the NT, the focus of this report is on NT residents who gave birth in the NT. Unless otherwise stated, the following key findings are for NT residents only							●			-		D	-
687	ヒト（エコチル調査）	Kishi, Reiko; Sasaki, Seiko; Yoshioka, Eiji; Yuasa, Motoyuki; Sata, Fumihiro; Saijo, Yasuaki; Kurahashi, Norie; Tamaki, Junko; Endo, Toshiaki; Sengoku, Kazuo; Nonomura, Katsuya; Minakami, Hisanori	Cohort profile: the Hokkaido study on environment and children's health in Japan	2011	Int J Epidemiol. 2011 Jun;40(3):611-8. doi: 10.1093/ije/dyq071. Epub 2010 May 26.	No abstract available							●		-		B	-
688	ヒト（発生毒性）	Jain, Ram B	Effect of pregnancy on the levels of selected perfluoroalkyl compounds for females aged 17-39 years: data from National Health and Nutrition Examination Survey 2003-2008	2013	J Toxicol Environ Health A. 2013;76(7):409-21. doi: 10.1080/15287394.2013.771547.	The presence of perfluoroalkyl chemicals (PFC) in maternal serum may pose a risk to the developing fetus. A large-scale study to evaluate the extent of exposure to PFC in pregnant and nonpregnant females in the United States has not been conducted. The impact of pregnancy on the concentration levels of perfluorohexane sulfonic acid (PFHxS), perfluorononanoic acid (PFNA), perfluorooctanoate (PFOA), and perfluorooctane sulfonate (PFOS) was assessed by analyzing data (n = 1079) from National Health and Nutrition Examination Survey (NHANES) for the years 2003-2008 for females aged 17-39 yr. While pregnant females possessed lower serum concentrations of all 4 PFC than nonpregnant females, only the differences for PFOS were significant (9.6 vs. 11.8 ng/ml). Those mothers who breast-fed at least one child displayed significantly lower levels of PFOA (2.6 vs. 3.1 ng/ml) than those with non-breast-fed infants. The concentration levels of PFNA and PFOA decreased with increase in number of live births. While levels of PFHxS and PFOS markedly fell over the period 2003-2008, the levels of PFNA rose over the same time period. There was nonlinear elevation in levels of PFHxS and PFOS with age. Smoking was associated with increased levels of PFNA and PFOA. There was a significant, positive association between total cholesterol and PFOS as well as for serum albumin with PFHxS and PFOS. Elevated levels of PFNA and PFOA were associated with a rise in serum protein. Further studies are needed to adequately explain why smoking was associated with increased levels of PFNA and PFOA.							●			-		B	-
689	ヒト（生殖毒性）	Bach, Cathrine Carlsen; Vested, Anne; Jørgensen, Kristian Tore; Bonde, Jens Peter Ellekilde; Henriksen, Tine Brink; Toft, Gunnar	Perfluoroalkyl and polyfluoroalkyl substances and measures of human fertility: a systematic review	2016	Crit Rev Toxicol. 2016 Oct;46(9):735-55. doi: 10.1080/10408444.2016.1182117. Epub 2016 Jun 8.	Perfluoroalkyl and polyfluoroalkyl substances (PFASs) are found widespread in the environment and humans. The relation of PFASs to fertility has now been examined in a relatively large number of epidemiologic studies and a synthesis is in order. The aim of this study was to assess the current human epidemiologic evidence on the association between exposure to PFASs and measures of human fertility, with particular emphasis on perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA). Systematic literature searches were initially conducted in MEDLINE and EMBASE and subsequently in references and citations of included papers. Studies were included if they assessed exposure to PFASs in biological samples in relation to reproductive hormones, semen characteristics, or time to pregnancy (TTP). Study characteristics and results were abstracted to predefined forms, and the studies were assessed for the risk of bias and confounding. Sixteen studies investigated the association between PFAS exposure in men and semen parameters, reproductive hormone levels, or TTP. There was a lack of consistent results among the numerous investigated exposure-outcome combinations. However, subtle associations between higher PFOS and lower testosterone or abnormal semen morphology cannot be excluded. Eleven studies assessed the association between PFAS exposure in women and TTP or reproductive hormones levels. Four of eight studies found prolonged TTP with higher PFOS or PFOA, but only one study found an association when restricting to nulliparous women. In men, there is little evidence of an association between PFAS exposure and semen quality or levels of reproductive hormones. For PFOS and PFOA, the literature indicates an association with female fecundability in parous women, which is most likely not causal.									●	レビュー		A	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
690	ヒト（生殖毒性）	Ou, Yanqiu; Zeng, Xiaowen; Lin, Shao; Bloom, Michael S; Han, Fengzhen; Xiao, Xiaohua; Wang, Hui; Matala, Rosemary; Li, Xiaohong; Qu, Yanji; Nie, Zhiqiang; Dong, Guanghui; Liu, Xiaoqing	Gestational exposure to perfluoroalkyl substances and congenital heart defects: A nested case-control pilot study	2021	Environ Int. 2021 Sep;154:106567. doi: 10.1016/j.envint.2021.106567. Epub 2021 Apr 23.	BACKGROUND: Accumulating evidence suggests that environmental pollutants may contribute to the occurrence of congenital heart defects (CHDs). However, no previous studies have evaluated the impact of perfluoroalkyl substances (PFAS), persistent environmental pollutants, on CHDs. This exploratory study aimed to generate testable hypotheses of the association between gestational PFAS and the risk of CHDs. METHODS: A nested case-control study was conducted in a cohort of 11,578 newborns. Exposure odds ratios were compared between 158 CHD cases and 158 non-malformed controls delivered at the same hospital, individually matched by maternal age (±5 years) and parity. Concentrations of 27 PFAS, including linear and branched isomers, were determined in maternal peripheral blood and cord blood plasma collected before and during delivery using a ultra-performance liquid chromatography coupled to mass spectrometry. Conditional logistic regression was utilized to evaluate associations between individual PFAS and the risk of CHDs, adjusted for confounding variables. RESULTS: Maternal gestational exposure to the highly branched perfluorooctanesulfonate (PFOS) isomer potassium 6-trifluoromethyperfluoroheptanesulfonate [6 m-PFOS, adjusted odds ratio (aOR) (95% CI) = 2.47(1.05,5.83)] and perfluorodecanoic acid [PFDA, aOR (95% CI) = 2.33(1.00,5.45)] were associated with increased odds of septal defects with statistical significance, while linear PFOS [aOR (95% CI) = 3.65(1.09,12.16)] and perfluoro-n-dodecanoic acid [PFDoA, aOR (95% CI) = 6.82(1.75, 26.61)] were associated with conotruncal defects. Effect estimates also suggested associations for higher maternal 6 m-PFOS and PFDA concentrations with ventricular septal defect. However, we did not observe these associations in cord blood. CONCLUSION: These exploratory findings suggested that gestational exposure to most PFAS, especially linear PFOS, 6 m-PFOS, PFDA, and PFDoA, was associated with greater risks for septal and conotruncal defects. However, a larger, adequately powered study is needed to confirm our findings, and to more comprehensively investigate the potential teratogenic effects of other more recently introduced PFAS, and on associations with individual CHD subtypes.								●	-		1	A	-
691	ヒト（生殖毒性）	Tarapore, Pheruza; Ouyang, Bin	Perfluoroalkyl Chemicals and Male Reproductive Health: Do PFOA and PFOS Increase Risk for Male Infertility? Int J Environ Res Public Health	2021	Int J Environ Res Public Health. 2021 Apr 5;18(7):3794. doi: 10.3390/ijerph18073794.	Poly- and perfluoroalkyl substances (PFAS) are manmade synthetic chemicals which have been in existence for over 70 years. Though they are currently being phased out, their persistence in the environment is widespread. There is increasing evidence linking PFAS exposure to health effects, an issue of concern since PFAS such as perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) bioaccumulate in humans, with a half-life of years. Many epidemiological studies suggest that, worldwide, semen quality has decreased over the past several decades. One of the most worrying effects of PFOS and PFOA is their associations with lower testosterone levels, similar to clinical observations in infertile men. This review thus focuses on PFOS/PFOA-associated effects on male reproductive health. The sources of PFAS in drinking water are listed. The current epidemiological studies linking increased exposure to PFAS with lowered testosterone and semen quality, and evidence from rodent studies supporting their function as endocrine disruptors on the reproductive system, exhibiting non-monotonic dose responses, are noted. Finally, their mechanisms of action and possible toxic effects on the Leydig, Sertoli, and germ cells are discussed. Future research efforts must consider utilizing better human model systems for exposure, using more accurate PFAS exposure susceptibility windows, and improvements in statistical modeling of data to account for the endocrine disruptor properties of PFAS.								●	-			B	-
692	ヒト（生殖毒性）	Wikström, Sverre; Hussein, Ghada; Lingroth Karlsson, Annika; Lindh, Christian H; Bornehag, Carl-Gustaf	Exposure to perfluoroalkyl substances in early pregnancy and risk of sporadic first trimester miscarriage	2021	Sci Rep. 2021 Feb 11;11(1):3568. doi: 10.1038/s41598-021-82748-6.	Many first trimester sporadic miscarriages are unexplained and the role of environmental exposures is unknown. The present aim was to study if levels of Perfluoroalkyl substances (PFASs) in early pregnancy are associated with unexplained, sporadic first trimester miscarriage. The study was performed within the Swedish SELMA pregnancy cohort. Seventy-eight women with non-recurrent first trimester miscarriage were included and 1449 women were available as live birth controls. Eight PFASs were measured in first trimester serum. A doubling of perfluorooctanoic acid (PFOA) exposure, corresponding to an inter-quartile increase, was associated with an odds ratio (95%CI) for miscarriage of 1.48 (1.09-2.01) when adjusting for parity, age and smoking. Analyses per quartiles of PFOA exposure indicated a monotonic dose response association with miscarriage. A similar, but not significant, pattern was observed for perfluorononanoic acid (PFNA). For other PFAS, there were no associations with miscarriage. We have previously shown associations between early pregnancy PFAS exposures and preeclampsia, as well as lower birth weight. Now we report an association between PFOA and miscarriage within the same cohort, which may suggest shared but unknown mechanisms. The study can only represent a period of early placentation and clinical pregnancy loss during the second half of the first trimester.								●	-			B	-
693	ヒト（発がん性）	Alexander, B. H.; Olsen, G. W.	Bladder Cancer in Perfluorooctanesulfonyl Fluoride Manufacturing Workers	2007	Ann Epidemiol. 2007 Jun;17(6):471-8. doi: 10.1016/j.annepidem.2007.01.036. Epub 2007 Apr 19.	Purpose	●	●		●	●				●	-		B	-
694	ヒト（発がん性）	Alexander, B. H.; Olsen, G. W.; Burris, J. M.; Mandel, J. H.; Mandel, J. S.	Mortality of employees of a perfluorooctanesulphonyl fluoride manufacturing facility	2020	Occup Environ Med. 2003 Oct;60(10):722-9. doi: 10.1136/oem.60.10.722.	AIM: To evaluate the mortality experience of a cohort of employees of a perfluorooctanesulphonyl fluoride (POSF) based fluorochemical production facility.METHODS: A retrospective cohort mortality study followed all workers with at least one year of cumulative employment at the facility. The jobs held by cohort members were assigned to one of three exposure subgroups; high exposed, low exposed, and non-exposed, based on biological monitoring data for perfluorooctane sulphonate (PFOS).RESULTS: A total of 145 deaths were identified in the 2083 cohort members. Sixty five deaths occurred among workers ever employed in high exposed jobs. The overall mortality rates for the cohort and the exposure subcohorts were lower than expected in the general population. Two deaths from liver cancer were observed in the workers with at least one year of high or low exposure (standardised mortality ratio (SMR) 3.08, 0.95 CI 0.37 to 11.10). The risk of death from bladder cancer was increased for the entire cohort (three observed, SMR 4.81, 0.95 CI 0.99 to 14.06). All three bladder cancers occurred among workers who held a high exposure job (SMR 12.77, 0.95 CI 2.63 to 37.35). The bladder cancer cases primarily worked in non-production jobs, including maintenance and incinerator and wastewater treatment plant operations.CONCLUSION: Workers employed in high exposure jobs had an increased number of deaths from bladder cancer; however it is not clear whether these three cases can be attributed to fluorochemical exposure, an unknown bladder carcinogen encountered during the course of maintenance work, and/or non-occupational exposures. With only three observed cases the possibility of a chance finding cannot be ruled out.	●	●		●	●				●	-		B	-
695	ヒト（発がん性）	American Cancer Society	Cancer facts and figures 2019 key statistics about kidney cancer	2020	Cancer Facts & Figures 2019, https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf	No abstract available	●	●							統計資料		D	-
696	ヒト（発がん性）	Barry, V.; Winquist, A.; Steenland, K.	Perfluorooctanoic acid (PFOA) exposures and incident cancers among adults living near a chemical plant	2019	Environ Health Perspect. 2013 Nov-Dec;121(11-12):1313-8 doi: 10.1289/ehp.1306615. Epub 2013 Sep 5.	BACKGROUND: Perfluorooctanoic acid (PFOA) is a synthetic chemical ubiquitous in the serum of U.S. residents. It causes liver, testicular, and pancreatic tumors in rats. Human studies are sparse.OBJECTIVE: We examined cancer incidence in Mid-Ohio Valley residents exposed to PFOA in drinking water due to chemical plant emissions.METHODS: The cohort consisted of adult community residents who resided in contaminated water districts or worked at a local chemical plant. Most participated in a 2005-2006 baseline survey in which serum PFOA was measured. We interviewed the cohort in 2008-2011 to obtain further medical history. Retrospective yearly PFOA serum concentrations were estimated for each participant from 1952 through 2011 Self-reported cancers were validated through medical records and cancer registry review. We estimated the association between cancer and cumulative PFOA serum concentration using proportional hazards models.RESULTS: Participants (n = 32,254) reported 2507 validated cancers (21 different cancer types). Estimated cumulative serum PFOA concentrations were positively associated with kidney and testicular cancer [hazard ratio (HR) = 1.10; 0.95 CI: 0.98, 1.24 and HR = 1.34; 0.95 CI: 1.00, 1.79, respectively, for 1-unit increases in ln-transformed serum PFOA]. Categorical analyses also indicated positive trends with increasing exposures for both cancers: for kidney cancer HRs for increasing exposure quartiles were 1.0, 1.23, 1.48, and 1.58 (linear trend test p = 0.18) and for testicular cancer, HRs were 1.0, 1.04, 1.91, 3.17 (linear trend test p = 0.04).CONCLUSIONS: PFOA exposure was associated with kidney and testicular cancer in this population. Because this is largely a survivor cohort, findings must be interpreted with caution, especially for highly fatal cancers such as pancreatic and lung cancer.	●	●		●		●			●	-		A	-
697	ヒト（発がん性）	Bartell, S. M.; Vieira, V. M.	Critical Review on PFOA, Kidney Cancer, and Testicular Cancer	2020	J Air Waste Manag Assoc. 2021 Jun;71(6):663-679. doi: 10.1080/10962247.2021.1909668.	The carcinogenicity of perfluorooctanoic acid (PFOA) has been reviewed previously by several different regulatory agencies and researchers, with contradictory conclusions–especially regarding epidemiological findings on kidney cancer and testicular cancer. In addition, previous dose-response assessments have focused primarily on evidence from animal studies. This critical review summarizes peer reviewed epidemiological studies on PFOA and cancers of the kidneys and testes, using modified Hill's criteria to assess the evidence for causation. We converted exposures to a common scale based on serum PFOA concentrations and applied meta-analysis to estimate the average increase in cancer risk reported by the studies with sufficient information to estimate serum PFOA. Using random effects meta-analysis, we found that the average relative increase in cancer risk per 10 ng/mL increase in serum PFOA for these studies is 0.16 (95% CI: 3%, 30%) for kidney cancer and 0.03 (95% CI: 2%, 4%) for testicular cancer. These associations are most likely causal, but results are limited by the small number of studies for testicular cancer, the overlapping study populations for several studies, and the lack of measured or modeled serum PFOA concentrations for several studies.	●	●								-		1	A	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献ランク①	文献ランク②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
698	ヒト（発がん性）	Bonefeld-Jorgensen, E. C.; Long, M.; Bossi, R.; Ayotte, P.; Asmund, G.; Krüger, T.; Ghisari, M.; Mulvad, G.; Kern, P.; Nzulumiki, P.; Dewailly, E.	Perfluorinated compounds are related to breast cancer risk in Greenlandic Inuit: a case control study	2011	Environ Health. 2011 Oct 6;10:88. doi: 10.1186/1476-069X-10-88.	BACKGROUND: Breast cancer (BC) is the most common cancer for women in the western world. From very few cases an extraordinary increase in BC was observed in the Inuit population of Greenland and Canada although still lower than in western populations. Previous data suggest that exposure to persistent organic pollutants (POPs) might contribute to the risk of BC. Rat studies showed that perfluorinated compounds (PFCs) cause significantly increase in mammary fibroadenomas. This study aimed at evaluating the association between serum levels of POPs/PFCs in Greenlandic Inuit BC cases and their controls, and whether the combined POP related effect on nuclear hormone receptors affect BC risk.METHODS: Thirty-one BC cases and 115 controls were sampled during 2000-2003 from various Greenlandic districts. The serum levels of POPs, PFCs, some metals and the combined serum POP related effect on estrogen- (ER), androgen- (AR) and Ah-receptor (AhR) transactivity were determined. Independent student t-test was used to compare the differences and the odds ratios were estimated by unconditional logistic regression models.RESULTS: We observed for the very first time a significant association between serum PFC levels and the risk of BC. The BC cases also showed a significantly higher concentration of polychlorinated biphenyls at the highest quartile. Also for the combined serum POP induced agonistic AR transactivity significant association to BC risk was found, and cases elicited a higher frequency of samples with significant POP related hormone-like agonistic ER transactivity. The AhR toxic equivalent was lowest in cases.CONCLUSIONS: The level of serum POPs, particularly PFCs, might be risk factors in the development of BC in Inuit. Hormone disruption by the combined serum POP related xenoestrogenic and xenoandrogenic activities may contribute to the risk of developing breast cancer in Inuit. Further investigations are needed to document these study conclusions.	●	●		●	●	●			●	-		C	-
699	ヒト（発がん性）	Bonefeld-Jørgensen, E. C.; Long, M.; Fredslund, S. O.; Bossi, R.; Olsen, J.	Breast cancer risk after exposure to perfluorinated compounds in Danish women: a case-control study nested in the Danish National Birth Cohort	2014	Cancer Causes Control. 2014 Nov;25(11):1439-48. doi: 10.1007/s10552-014-0446-7. Epub 2014 Aug 23.	OBJECTIVE: Animal studies have indicated that perfluoroalkylated substances (PFAS) increase mammary fibroadenomas. A recent case-control study in Greenlandic Inuit women showed an association between the PFAS serum levels and breast cancer (BC) risk. The present study evaluates the association between serum levels of PFAS in pregnant Danish women and the risk of premenopausal BC during a follow-up period of 44849 years using prospectively collected exposure data during the pregnancy.METHODS: Questionnaire and blood samples were taken during 1996-2002 and at the end of follow-up, all 250 BC cases and 233 frequency-matched controls were chosen for further analyses. Serum levels of ten perfluorocarboxylated acids, five perfluorosulfonated acids, and one sulfonamide (perflurooctane-sulfonamide, PFOSA) were determined by liquid chromatography-tandem mass spectrometry with electrospray ionization in negative mode. Computer-assisted telephone interviews taken during pregnancy provided data on potential confounders.RESULTS: Weak positive and negative insignificant associations were found between BC risk and levels of perfluorooctane sulfonamide (PFOSA) and perfluorohexanesulfonate (PFHxS), respectively. Grouped into quintile, the BC cases had a significant positive association with PFOSA at the highest quintiles and a negatively association for PFHxS. Sensitivity analyses excluding uncertain cases caused stronger data for PFOSA and weaker for PFHxS. No further significant associations were observed.CONCLUSIONS: This study does not provide convincing evidence for a causal link between PFAS exposures and premenopausal BC risks 44849 years later.	●	●		●					●	-		B	-
700	ヒト（発がん性）	C8 Science Panel	C8 study results - Status reports	2012	Available online at http://www.c8sciencepanel.org/index.html	No abstract available	●	●								C8 science panel ウェブサイト公表資料。対象外とする		D	-
701	ヒト（発がん性）	Chang, E. T.; Adami, H. O.; Boffetta, P.; Cole, P.; Starr, T. B.; Mandel, J. S.	A critical review of perfluorooctanoate and perfluorooctanesulfonate exposure and cancer risk in humans [Review]	2014	Crit Rev Toxicol. 2014 May;44 Suppl 1:1-81. doi: 10.3109/10408444.2014.905767. Epub 2014 May 5.	Perfluorooctanoate (PFOA) and perfluorooctanesulfonate (PFOS) are ubiquitous synthetic chemicals with no known effect on human cancer development. This article systematically and critically reviews the epidemiologic evidence regarding the association between PFOA and PFOS exposure and cancer risk in humans. Eighteen epidemiologic studies - eight of PFOA, four of PFOS, and six of both PFOA and PFOS - have estimated associations of exposure to these chemicals with cancer incidence or mortality, with studies equally divided between occupational and nonoccupational settings. Although some statistically significant positive associations have been reported, for example, with cancers of the prostate, kidney, testis, and thyroid, the majority of relative risk estimates for both PFOA and PFOS have been between 0.5 and 2 (with 0.95 confidence intervals including 1.0), inconsistently detected across studies, counterbalanced by negative associations, not indicative of a monotonic exposure-response relationship, and not coherent with toxicological evidence in animals, in which the primary target organs are the liver, testis (Leydig cells), and pancreas (acinar cells). Many positive associations with PFOA exposure were detected in community settings without occupational exposure and were not supported by results in exposed workers. Given that occupational exposure to PFOA and PFOS is one to two orders of magnitude higher than environmental exposure, the discrepant positive findings are likely due to chance, confounding, and/or bias. Taken together, the epidemiologic evidence does not support the hypothesis of a causal association between PFOA or PFOS exposure and cancer in humans.	●	●		●		●				-	1	A	-
702	ヒト（発がん性）	Cohn, B. A.; La Merrill, M. A.; Krigbaum, N. Y.; Wang, M.; Park, J. S.; Petreas, M.; Yeh, G.; Hovey, R. C.; Zimmermann, L.; Cirillo, P. M.	In utero exposure to poly- and perfluoroalkyl substances (PFASs) and subsequent breast cancer	2020	Reprod Toxicol. 2020 Mar;92:112-119. doi: 10.1016/j.reprotox.2019.06.012. Epub 2019 Jul 16.	We tested the hypothesis that maternal perinatal serum levels of poly and perfluoroalkyl substances (PFASs) predict risk for breast cancer in daughters in a 54-year follow-up of 9300 daughters born 1959-1967 in the Child Health and Development Studies pregnancy cohort. Total cholesterol and PFASs were measured in archived maternal perinatal serum for 102 daughter breast cancer cases diagnosed by age 52, and 310 controls matched on birth year and blood draw trimester. High maternal N-ethyl-perfluorooctane sulfonamido acetic acid (EtFOSAA), a precursor of perfluorooctane sulfonic acid (PFOS), in combination with high maternal total cholesterol predicted a 3.6-fold increased risk of breast cancer (pinteraction<0.05). Conversely, maternal PFOS was associated with decreased daughters' breast cancer risk. Predictions were robust to alternative modeling and independent of other maternal factors. Future generations continue to be exposed to ubiquitous, persistent PFASs. These findings are relevant to breast cancer prevention if confirmed experimentally and where possible, in additional epidemiology studies of internal doses of PFASs and other chemical mixtures especially during vulnerable windows in early life.	●	●	●							-		B	-
703	ヒト（発がん性）	Ducatman, A.; Zhang, J.; Fan, H.	Prostate-specific antigen and perfluoroalkyl acids in the C8 health study population	2015	J Occup Environ Med. 2015 Jan;57(1):111-4. doi: 10.1097/JOM.0000000000000319.	PURPOSE: To inform questions raised by inconsistent findings regarding an association between perfluoroalkyl acids (PFAAs) and prostate cancer by assessing the relationship of PFAAs in human serum to prostate-specific antigen (PSA).MATERIALS AND METHODS: Using 2005 to 2006 survey data from a large survey population, we compared serum PFAA concentrations in adult males with PSA concentrations adjusted for risk factors including age, body mass index, smoking status, and socioeconomic status.RESULTS: Perfluoroalkyl acids are not consistently associated with PSA concentration in general, or with PSA more than 4.0.DISCUSSION: These findings do not provide evidence that PFAA exposure is associated with PSA.	●	●		●					●	-		B	-
704	ヒト（発がん性）	Eriksen, K. T.; Sørensen, M.; Mclaughlin, J. K.; Lipworth, L.; Tjønneland, A.; Overvad, K.; Raaschou-Nielsen, O.	Perfluorooctanoate and perfluorooctanesulfonate plasma levels and risk of cancer in the general Danish population	2009	J Natl Cancer Inst. 2009 Apr 15;101(8):605-9. doi: 10.1093/jnci/djp041. Epub 2009 Apr 7.	Perfluorooctanoate and perfluorooctanesulfonate are used in many industrial products and have been widely detected in human blood. Both chemicals are associated with tumor development in animal studies, but data on carcinogenic potential in humans are sparse. We investigated the association between plasma levels of perfluorooctanoate and perfluorooctanesulfonate and cancer risk within a prospective Danish cohort of participants with no previous cancer diagnosis at enrollment. From enrollment, between December 1, 1993, and May 31, 1997, and through July 1, 2006, we identified 713 participants with prostate cancer, 332 with bladder cancer, 128 with pancreatic cancer, and 67 with liver cancer in the entire cohort and we selected a comparison subcohort of 772 Plasma concentrations of perfluorooctanoate and perfluorooctanesulfonate were measured in each participant by use of high-pressure liquid chromatography coupled to tandem mass spectrometry. We found no clear differences in incidence rate ratios for these cancers in relation to plasma concentrations of perfluorooctanoate or perfluorooctanesulfonate. A 30%-40% increase in risk estimates for prostate cancer was observed for the three upper quartiles of perfluorooctanesulfonate concentration compared with the lowest quartile (eg, for the lowest vs the fourth quartile, incidence rate ratio = 1.38, 0.95 confidence interval = 0.99 to 1.93). Plasma concentrations of perfluorooctanoate and perfluorooctanesulfonate in the general Danish population appear not to be associated with risk of prostate, bladder, pancreatic, or liver cancer.	●	●		●	●	●			●	-	1	A	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
705	ヒト（発がん性）	Fry, K.; Power, M. C.	Persistent organic pollutants and mortality in the United States, NHANES 1999-2011	2017	Environ Health. 2017 Oct 10;16(1):105. doi: 10.1186/s12940-017-0313-6.	BACKGROUND: Persistent organic pollutants (POPs) are environmentally and biologically persistent chemicals that include polybrominated diphenyl ethers (PBDEs), per- and polyfluoroalkyl substances (PFASs), polychlorinated biphenyls (PCBs), and organochlorine (OC) pesticides. Currently, data on the associations between exposure to POPs and the risk of mortality in the U.S. population is limited. Our objective was to determine if higher exposure to POPs is associated with greater risk of all-cause, cancer, heart/cerebrovascular disease, or other-cause mortality.METHODS: Analyses included participants aged 60 years and older from the 1999-2006 National Health and Nutrition Examination Surveys (NHANES). We included 483 participants for analyses of PBDEs, 1043 for PFASs, and 461 for PCBs, and 1428 for OC pesticides. Exposures to POPs were estimated using biomarkers measured in serum. Mortality status through December 31, 2011 was obtained from public-use, linked mortality files. We used Cox proportional hazard models to quantify the associations of interest. Where we observed an association, we explored effect modification by sex, body mass index, smoking status, and albuminuria. We also explored the combined effect of PBDEs and OC pesticides in the subsample of participants with measures of both analytes.RESULTS: Serum measurements of PBDEs, PFASs, and PCBs were not clearly associated with increased all-cause or cause-specific mortality in older Americans. Beta-hexachlorocyclohexane was associated with an increased risk of all-cause mortality [HR per 1 SD increase =1.18, 95% CI = 1.01, 1.38]. Oxychlordane [HR = 1.15 95% CI 1.06, 1.25], p,p'-DDE [HR = 1.12, 95% CI = 1.02, 1.23], trans-nonachlor [HR = 1.11, 95% CI = 1.04, 1.18], and beta-hexachlorocyclohexane [HR = 1.25, 95% CI = 1.03, 1.52] were associated with increased risk of other-cause mortality. Exploratory analyses suggested associations between OC pesticides and other-cause mortality were modified by sex. Exploratory analyses also suggested that the combination of high PBDE and high OC pesticide exposure had a stronger than expected adverse effect on all-cause mortality.CONCLUSION: Higher exposure to beta-hexachlorocyclohexane, an OC pesticide, is associated with increased all-cause mortality and higher exposure to four OC pesticides is associated with increased non-cancer, non-heart/cerebrovascular disease mortality in U.S. adults 60 years or older. These associations may be modified by sex or exposure to other POPs.	●	●							-		B	-
706	ヒト（発がん性）	Ghisari, M; Long, M; Røge, DM; Olsen, J; Bonefeld-Jørgensen, EC.	Polymorphism in xenobiotic and estrogen metabolizing genes, exposure to perfluorinated compounds and subsequent breast cancer risk: A nested case-control study in the Danish National Birth Cohort	2000	Environ Res. 2017 Apr;154:325-333. doi: 10.1016/j.envres.2017.01.020. Epub 2017 Feb 2.	In the present case-cohort study based on prospective data from Danish women, we aimed to estimate the main effect of polymorphisms in genes known to be involved in the steroid hormone metabolic pathway and xenobiotic metabolism on the risk of developing breast cancer. We also studied a possible effect measure modification between genotypes and levels of serum perfluoroalkylated substances (PFASs) on the risk to breast cancer. We have previously reported a weak association between serum PFASs levels and the risk of breast cancer for this study population of Danish pregnant nulliparous women as well as in a smaller case-control study of Greenlandic women. The study population consisted of 178 breast cancer cases and 233 controls (tabnulliparous and frequency matched on age) nested within the Danish National Birth Cohort (DNBC), which was established in 1996-2002. Blood samples were drawn at the time of enrollment (6-14 week of gestation). Serum levels of 10 perfluorocarboxylated acids (PFCAs), 5 perfluorosulfonated acids (PFSAs) and 1 sulfonamide (perflurooctane-sulfonamide, PFOSA) were measured. Genotyping was conducted for CYP1A1 (Ile462Val; rs1048943), CYP1B1 (Leu432Val; rs1056836), COMT (Val158Met; rs4680), CYP17A1 (A1→ A2; rs743572); CYP19A1 (C→T; rs10046) by the TaqMan allelic discrimination method. In overall, no significant associations were found between the investigated polymorphisms and the risk of breast cancer in this study among Danish women. The previously found association between PFOSA and risk of breast cancer did vary between different genotypes, with significantly increased risk confined to homozygous carriers of the following alleles: COMT (Met), CYP17 (A1) and CYP19 (C). Conclusion: Our results indicate that polymorphisms in COMT, CYP17 and CYP19 which are involved in estrogen biosynthesis and metabolism can modulate the potential effects of PFOSA exposure on the development of breast cancer.	●								-		B	-
707	ヒト（発がん性）	Gilliland, FD; Mandel, JS.	Mortality among employees of a perfluorooctanoic acid production plant	2017	J Occup Med. 1993 Sep;35(9):950-4. doi: 10.1097/00043764-199309000-00020.	Perfluorooctanoic acid (PFOA) has been found at low levels (10 to 100 parts per billion) in sera of the general population and at higher levels in occupationally exposed workers. Although PFOA has been reported to be a promoter of rodent hepatocarcinogenesis and to alter reproductive hormones in humans and rodents, there is little information on human health effects associated with PFOA exposure. The present study examined the relationship between PFOA and mortality using a retrospective cohort mortality design. The cohort consisted of 2788 male and 749 female workers employed between 1947 and 1983 at a plant that produced PFOA. The all-causes standardized mortality ratio was .75 (95% confidence interval [CI], .56 to .99) for women and .77 (95% CI, .69 to .86) for men. Among men the cardiovascular standardized mortality rate was .68 (95% CI, .58 to .80) and the all-gastrointestinal diseases was .57 (95% CI, .29 to .99). There was no significantly increased cause-specific standardized mortality ratio for either men or women. Ten years of employment in exposed jobs was associated with a 3.3-fold increase (95% CI, 1.02 to 10.6) in prostate cancer mortality compared to no employment in PFOA production. There were only six prostate cancer deaths overall and four among the exposed workers; thus, the results must be interpreted cautiously. If prostate cancer mortality is related to PFOA, PFOA may increase prostate cancer mortality by altering reproductive hormones in male workers.	●								-		B	-
708	ヒト（発がん性）	Girardi, Paolo; Merler, Enzo	A mortality study on male subjects exposed to polyfluoroalkyl acids with high internal dose of perfluorooctanoic acid	2016	Environ Res. 2019 Dec;179(Pt A):108743. doi: 10.1016/j.envres.2019.108743. Epub 2019 Sep 14.	OBJECTIVES: The aim of the present study was to examine the association between exposure to polyfluoroalkyl substances (PFASs) and mortality (1970-2018) in a cohort of 462 male employees who had worked at least six months before 2009 for a factory (14,658 person-years; 107 deaths, average follow-up time 31.7 years), which had been producing perfluorooctanoic acid (PFOA), perfluorooctanesulfonyl fluoride (PFOS) and other chemicals since 1968. METHODS: Employees were classified as follows: 1) by probability of exposure to PFASs; 2) by tertiles of PFOA serum concentrations. In a fraction (n = 120) of workers measurements of internal PFOA serum concentration were used to predict a cumulative serum PFOA concentration of each cohort member. Mortality rates were compared to that of the regional population using the standardized mortality ratio (SMR), and to that of the workers of a nearby metalworking factory in terms of risk ratio (RR), across categories of probability of PFASs exposure and tertiles of cumulative serum PFOA concentrations. RESULTS: Internal PFOA serum concentration among 120 workers in the 2000-2013 period was very high (Geometric Mean: 4048 ng/mL; range 19-91,900 ng/mL). The mortality of the chemical cohort was increased for liver cancer (SMR: 2.32; CI: 1.11-4.87), malignant neoplasm of lymphatic and haematopoietic tissue (SMR: 2.26; CI: 1.08-4.73). In the comparison with the cohort of workers from the metalworking factory, the RRs for mortality of the cohort were increased for overall mortality (RR: 1.42; CI: 1.12-1.79), diabetes (RR: 5.95; CI: 1.08-32.8), liver cancer (RR: 6.69; CI: 1.71-26.2) and liver cirrhosis (RR: 3.87; CI: 1.18-12.7). Mortality for these causes increased in association with probability of PFASs exposure and with tertiles of cumulative PFOA serum concentrations. CONCLUSION: The present is a small observational study with limited control over confounding factors. The cohort showed increased mortality for all causes and subjects in the highest cumulative internal dose of PFOA had a statistically significant increase for mortality of liver cancer, liver cirrhosis, diabetes, malignant neoplasms of lymphatic and haematopoietic tissue in both comparisons. Toxicological studies on PFOA and PFOS provide support for causality for the observed association with the risk for liver cirrhosis and liver cancer.	●	●							-		B	-
709	ヒト（発がん性）	Hardell, E.; Kärrman, A.; van Bavel, B.; Bao, J.; Carlberg, M.; Hardell, L.	Case-control study on perfluorinated alkyl acids (PFAAs) and the risk of prostate cancer	2014	Environ Int. 2014 Feb;63:35-9. doi: 10.1016/j.envint.2013.10.005. Epub 2013 Nov 16.	Perfluorinated alkyl acids (PFAAs) are emerging environmental contaminants. Possible health effects for humans include increased risk for cancer but the knowledge is limited. In this study serum concentrations of certain perfluorinated sulfonates (PFHxS and PFOS) and carboxylates (PFOA, PFNA, PFDA, PFUnDA) were analyzed among 201 cases with prostate cancer and 186 population based control subjects. All blood samples were collected during 2007-2011 and no case had been treated with radio- or chemotherapy before enrolment in the study. The blood concentrations did not differ statistically significant between cases and controls except for PFDA with higher concentration among the cases (p=0.03). Analyses based on Gleason score and prostate specific antigen (PSA) level did not change the results. Heredity was a risk factor for prostate cancer yielding odds ratio (OR)=1.8, 0.95 confidence interval (CI)=1.01-3.1. The analyzed PFAAs yielded statistically significant higher ORs in cases with a first degree relative reporting prostate cancer, e.g., PFOA gave OR=2.6, 0.95 CI=1.2-6.0 and PFOS gave OR=2.7, 0.95 CI=1.04-6.8. The results showed a higher risk for prostate cancer in cases with heredity as a risk factor. In further studies interaction between gene and environment should be considered.	●	●	●	●				●	-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
710	ヒト（発がん性）	Innes, Kim E; Wimsatt, Jeffrey H; Frisbee, Stephanie; Ducatman, Alan M	Inverse association of colorectal cancer prevalence to serum levels of perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) in a large Appalachian population	2020	BMC Cancer. 2014 Jan 27;14:45. doi: 10.1186/1471-2407-14-45.	BACKGROUND: Perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) are persistent environmental contaminants that affect metabolic regulation, inflammation, and other factors implicated in the development and progression of colorectal cancer (CRC). However, the link between these compounds and CRC remains unknown. In this cross-sectional study, we investigated the association of CRC diagnosis to PFOA and PFOS blood levels in a large Appalachian population. METHODS: Participants were 47,359 adults ≥ 21 years of age and residing in six PFOA-contaminated water districts in the mid-Ohio Valley (N = 47,151 cancer-free adults, 208 cases of primary CRC). All participants completed a comprehensive health survey between 2005 and 2006; serum levels of PFOA, PFOS, and a range of other blood markers were also measured. Medical history was assessed via self report and cancer diagnosis confirmed via chart review. RESULTS: CRC showed a strong inverse, dose-response association with PFOS serum levels (odds ratio (OR) adjusted for potential confounders = 0.2, 95% confidence interval (CI) 0.2,0.3) for highest vs. lowest quartile of PFOS, P-trend < 0.00001) and a significant, but more modest inverse association with PFOA (adjusted OR = 0.6 (CI 0.4, 0.9) for highest vs. lowest quartile, P-trend = 0.001). These inverse associations were stronger in those diagnosed within the previous 6 years and resident in the same water district for a minimum of 10-15 years preceding assessment. The relationship between PFOA and CRC was also more pronounced in men and leaner adults, and showed a stronger linear trend at lower exposure levels. CONCLUSIONS: In this large cross-sectional study, we found a strong, inverse association between PFOS and likelihood of CRC diagnosis and a significant, although more modest inverse association between PFOA and CRC. If confirmed in prospective investigations, these findings may aid in identifying new strategies for CRC prevention and treatment and inform future studies regarding mechanisms underlying CRC pathogenesis.	●	●		●					-		B	-
711	ヒト（発がん性）	Lin, H. W.; Feng, H. X.; Chen, L.; Yuan, X. J.; Tan, Z.	Maternal exposure to environmental endocrine disruptors during pregnancy is associated with pediatric germ cell tumors	2020	Nagoya J Med Sci. 2020 May;82(2):323-333. doi: 10.18999/nagjms.82.2.315.	Environmental endocrine disruptors (EEDs) are natural or synthetic chemical compounds that interfere with normal endocrine function in both wildlife and humans. Previous studies have indicated that EEDs may contribute to oncogenesis. This study explores the relationship between EEDs and pediatric germ cell tumors (GCTs). A case-control study was conducted in 84 pediatric patients from 2014 to 2017, including 42 subjects with immature teratoma, yolk sac tumor, or germinoma, and 42 controls who experienced pneumonia or trauma. Serum PFASs, including PFBS, PFHpA, PFHxS, PFOA, PFOS, PFNA, PFDA, PFUA, PFOSA, and PFDoA, were measured in each subject, and their history of possible EED exposure was reviewed. Six of the 10 measured PFASs were significantly increased in the GCT group relative to the control group. With respect to lifestyle history, only PFHxS levels were statistically significantly associated with GCTs as determined by logistic regression analysis. The odds ratio for a 1 ng/L increase in PFHxS was 19.47 (95% CI: 4.20-90.26). Furthermore, in the GCT and control groups, both parental consumption of barbecued foods and hair dye use among parents were significantly correlated with elevated serum PFHxS levels (ρ = 0.383, 0.325 in the patient group and ρ = 0.370, 0.339 in the control group; p < 0.05). Our study confirmed that children with GCTs from our institute had relatively high serum levels of PFASs relative to those of tumor-free pediatric patients. Serum PFHxS levels were independently associated with germ cell tumor occurrence.	●	●							-		B	-
712	ヒト（発がん性）	Lundin, JI; Alexander, BH; Olsen, GW; Church, TR.	Ammonium Perfluorooctanoate Production and Occupational Mortality	2009	Epidemiology. 2009 Nov;20(6):921-8. doi: 10.1097/EDE.0b013e3181b5f395.	Background: Perfluorooctanoate (PFOA) is a synthetic chemical widely detectable in blood of nonoccupationally exposed persons. Its human health effects are not well-characterized. Methods: We conducted a mortality study in a cohort of 3993 employees of an ammonium perfluorooctanoate (APFO) manufacturing facility. APFO rapidly dissociates to PFOA in blood. We estimated standardized mortality ratios (SMRs) compared with the general population, and fit time-dependent Cox regression models to estimate the risks using an internal-cohort referent population. A priori diseases of interest were liver, pancreatic, prostate, and testicular cancer; cirrhosis of the liver; and cerebrovascular disease. Results: APFO exposure was not associated with liver, pancreatic or testicular cancer or with cirrhosis of the liver. SMRs (95% CI) for prostate cancer with no, probable and definite exposure strata were 0.4 (0.1–0.9), 0.9 (0.4–1.8), and 2.1 (0.4–6.1), respectively, and for cerebrovascular disease 0.5 (0.3–0.8), 0.7 (0.4–1.1), and 1.6 (0.5–3.7), respectively. The diabetes SMR for probable exposure was 2.0 (1.0–3.2). Compared with an internal referent population of nonexposed workers, moderate or high exposures to ammonium perfluorooctanoate were positively associated with prostate cancer (HR = 3.0 [0.9–9.7] and 6.6 [1.1–37.7], respectively) and with cerebrovascular disease (1.8 [0.9–3.1] and 4.6 [1.3–17.0], respectively). Diabetes was associated with moderate exposure 3.7 (1.4–10.1); no deaths from diabetes occurred in workers with high exposure. Conclusion: We did not observe ammonium perfluorooctanoate exposure to be associated with liver, pancreatic, and testicular cancer or cirrhosis of the liver. Exposure was associated (albeit inconsistently) with prostate cancer, cerebrovascular disease, and diabetes.	●	●		●		●			-		B	-
713	ヒト（発がん性）	Mancini, F. R.; Cano-Sancho, G.; Gambaretti, J.; Marchand, P.; Boutron-Ruault, M. C.; Severi, G.; Arveux, P.; Antignac, J. P.; Kvaskoff, M.	Perfluorinated alkylated substances serum concentration and breast cancer risk: Evidence from a nested case-control study in the French E3N cohort	2019	Int J Cancer. 2020 Feb 15;146(4):917-928. doi: 10.1002/ijc.32357. Epub 2019 May 3.	Endocrine-disrupting chemicals are proposed to increase breast cancer (BC) incidence. Perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA), two perfluorinated alkylated substances (PFASs), are suspected to be ubiquitously present in the blood of human population worldwide. We investigated the associations between serum concentrations of these substances and BC risk. Etude Epidémiologique auprès de femmes de l'Education Nationale is a cohort of 98995 French women born in 1925-1950 and followed up since 1990 We sampled 194 BC cases and 194 controls from women with available blood samples. Serum concentrations of PFASs were measured by liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). Adjusted conditional logistic regression models were used to estimate odds ratios (ORs) and 0.95 confidence intervals (CIs). All statistical tests were two sided. While PFASs concentrations were not associated with BC risk overall, we found positively linear associations between PFOS concentrations and the risk of ER+ (3rd quartile: OR = 2.22 [CI = 1.05-4.69]; 4th quartile: OR = 2.33 [CI = 1.11-4.90]); Ptrend = 0.04) and PR+ tumors (3rd quartile: OR = 2.47 [CI = 1.07-5.65]; 4th quartile: OR = 2.76 [CI = 1.21-6.30]; Ptrend = 0.02). When considering receptor-negative tumors, only the 2nd quartile of PFOS was associated with risk (ER-: OR = 15.4 [CI = 1.84-129.19]; PR-: OR = 3.47 [CI = 1.29-9.15]). While there was no association between PFOA and receptor-positive BC risk, the 2nd quartile of PFOA was positively associated with the risk of receptor-negative tumors (ER-: OR = 7.73 [CI = 1.46-41.08]; PR-: OR = 3.44 [CI = 1.30-9.10]). PFAS circulating levels were differentially associated with BC risk. While PFOS concentration was linearly associated with receptor-positive tumors, only low concentrations of PFOS and PFOA were associated with receptor-negative tumors. Our findings highlight the importance of considering exposure to PFASs as a potential risk factor for BC.	●	●	●					●	-		1	A	-
714	ヒト（発がん性）	Raleigh, Katherine K; Alexander, Bruce H; Olsen, Geary W; Ramachandran, Gurumurthy; Morey, Sandy Z; Church, Timothy R; Logan, Perry W; Scott, Laura L F; Allen, Elizabeth M	Mortality and cancer incidence in ammonium perfluorooctanoate production workers	2014	Occup Environ Med. 2014 Jul;71(7):500-6. doi: 10.1136/oemed-2014-102109. Epub 2014 May 15.	OBJECTIVE: To evaluate mortality and cancer incidence in a cohort of ammonium perfluorooctanoate (APFO) exposed workers. METHODS: We linked a combined cohort (n=9027) of employees from APFO and non-APFO production facilities in Minnesota to the National Death Index and to cancer registries of Minnesota and Wisconsin. Industrial hygiene data and expert evaluation were used to create a task-based job exposure matrix to estimate APFO exposure. Standardised mortality ratios were estimated using Minnesota population rates. HRs and 95% CIs for time-dependent cumulative APFO exposure were estimated with an extended Cox model. A priori outcomes of interest included cancers of the liver, pancreas, testes, kidney, prostate and breast, and mortality from cardiovascular, cerebrovascular and chronic renal diseases. RESULTS: Mortality rates in the APFO-exposed cohort were at or below the expected, compared with Minnesota. The HR for dying from the cancer and non-cancer outcomes of interest did not show an association with APFO exposure. Similarly, there was little evidence that the incident cancers were associated with APFO exposure. Compared to the non-exposed population, modestly elevated, but quite imprecise HRs were observed in the higher-exposure quartiles for bladder cancer (HR=1.66, 95% CI 0.86 to 3.18) and pancreatic cancer (HR=1.36, 95% CI 0.59 to 3.11). No association was observed between APFO exposure and kidney, prostate or breast cancers. CONCLUSIONS: This analysis did not support an association between occupational APFO exposure and the evaluated health endpoints, however, the study had limited power to evaluate some conditions of interest.	●	●		●					-		C	-
715	ヒト（発がん性）	Shearer, J. J.; Callahan, C. L.; Calafat, A. M.; Huang, W. Y.; Jones, R. R.; Sabbisetti, V. S.; Freedman, N. D.; Sampson, J. N.; Silverman, D. T.; Purdue, M. P.; Hofmann, J. N.	Serum concentrations of per- and polyfluoroalkyl substances and risk of renal cell carcinoma	2020	J Natl Cancer Inst. 2021 May 4;113(5):580-587. doi: 10.1093/jnci/djaa143.	Background: Per- and polyfluoroalkyl substances (PFAS) are highly persistent chemicals that have been detected in the serum of over 0.98 of the US population. Studies among highly exposed individuals suggest an association with perfluorooctanoic acid (PFOA) exposure and kidney cancer. It remains unclear whether PFOA or other PFAS are renal carcinogens or if they influence risk of renal cell carcinoma (RCC) at concentrations observed in the general population.	●	●						●	-		1	A	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
716	ヒト（発がん性）	Steenland, Kyle; Fletcher, Tony; Stein, Cheryl R; Bartell, Scott M; Darrow, Lyndsey; Lopez-Espinosa, Maria-Jose; Barry Ryan, P; Savitz, David A	Review: Evolution of evidence on PFOA and health following the assessments of the C8 Science Panel [Review]	2013	Environ Int. 2020 Dec;145:106125. doi: 10.1016/j.envint.2020.106125. Epub 2020 Sep 18.	BACKGROUND: The C8 Science Panel was composed of three epidemiologists charged with studying the possible health effects of PFOA in a highly exposed population in the mid-Ohio Valley. The Panel determined in 2012 there was a 'probable link' (i.e., more probable than not based on the weight of the available scientific evidence) between PFOA and high cholesterol, thyroid disease, kidney and testicular cancer, pregnancy-induced hypertension, and ulcerative colitis. OBJECTIVE: Here, former C8 Science Panel members and collaborators comment on the PFOA literature regarding thyroid disorders, cancer, immune and auto-immune disorders, liver disease, hypercholesterolemia, reproductive outcomes, neurotoxicity, and kidney disease. We also discuss developments regarding fate and transport, and pharmacokinetic models, and discuss causality assessment in cross-sectional associations among low-exposed populations. DISCUSSION: For cancer, the epidemiologic evidence remains supportive but not definitive for kidney and testicular cancers. There is consistent evidence of a positive association between PFOA and cholesterol, but no evidence of an association with heart disease. There is evidence for an association with ulcerative colitis, but not for other auto-immune diseases. There is good evidence that PFOA is associated with immune response, but uneven evidence for an association with infectious disease. The evidence for an association between PFOA and thyroid and kidney disease is suggestive but uneven. There is evidence of an association with liver enzymes, but not with liver disease. There is little evidence of an association with neurotoxicity. Suggested reductions in birthweight may be due to reverse causality and/or confounding. Fate and transport models and pharmacokinetic models remain central to estimating past exposure for new cohorts, but are difficult to develop without good historical data on emissions of PFOA into the environment. CONCLUSION: Overall, the epidemiologic evidence remains limited. For a few outcomes there has been some replication of our earlier findings. More longitudinal research is needed in large populations with large exposure contrasts. Additional cross-sectional studies of low exposed populations may be less informative.	●	●							●	-		B	-
717	ヒト（発がん性）	Steenland, Kyle; Woskie, Susan	Cohort mortality study of workers exposed to perfluorooctanoic acid	2012	Am J Epidemiol. 2012 Nov 15;176(10):909-17. doi: 10.1093/aje/kws171. Epub 2012 Oct 18.	Perfluorooctanoic acid (PFOA) is persistent in the human body; the general population has serum levels of approximately 4 ng/mL. It causes tumors of the liver, pancreas, and testicles in rodents. The authors studied the mortality of 5,791 workers exposed to PFOA at a DuPont chemical plant in West Virginia, using a newly developed job exposure matrix based on serum data for 1,308 workers from 1979-2004. The estimated average serum PFOA level was 350 ng/mL. The authors used 2 referent groups: other DuPont workers in the region and the US population. In comparison with other DuPont workers, cause-specific mortality was elevated for mesothelioma (standardized mortality ratio (SMR) = 2.85, 95% confidence interval (CI): 1.05, 6.20), diabetes mellitus (SMR = 1.90, 95% CI: 1.35, 2.61), and chronic renal disease (SMR = 3.11, 95% CI: 1.66, 5.32). Significant positive exposure-response trends occurred for both malignant and nonmalignant renal disease (12 and 13 deaths, respectively). PFOA is concentrated in the kidneys of rodents, and there are prior findings of elevated kidney cancer in this cohort. Multiple-cause mortality analyses tended to support the results of underlying-cause analyses. No exposure-response trend was seen for diabetes or heart disease mortality. In conclusion, the authors found evidence of positive exposure-response trends for malignant and nonmalignant renal disease. These results were limited by small numbers and restriction to mortality data, which are of limited relevance for several nonfatal outcomes of a priori interest.	●	●		●		●				-		B	-
718	ヒト（発がん性）	Tsai, M. S.; Chang, S. H.; Kuo, W. H.; Kuo, C. H.; Li, S. Y.; Wang, M. Y.; Chang, D. Y.; Lu, Y. S.; Huang, C. S.; Cheng, A. L.; Lin, C. H.; Chen, P. C.	A case-control study of perfluoroalkyl substances and the risk of breast cancer in Taiwanese women	2020	Environ Int. 2020 Sep;142:105850. doi: 10.1016/j.envint.2020.105850. Epub 2020 Jun 21.	Breast cancer (BC) is a common cancer in women worldwide; however, the incidence of BC is increasing in younger women, possibly associated with the environment. Perfluoroalkyl substances (PFAS) are one of endocrine disruptors that accumulate in environment and impact human health. This study aimed to investigate whether the PFAS and BC are associated. We enrolled 120 BCE patients and 119 controls at National Taiwan University Hospital (NTUH) and also collected bio-specimen and questionnaire from 2013 to 2015 All subjects' plasma PFAS levels were analyzed by ultra-performance liquid chromatography tandem mass spectrometry method with electrospray ionization (UHPLC-ESI-MS/MS). A logistic regression model was used to estimate the association between PFAS and BC. In the ≤50 years age group, the adjusted odds ratio (OR) was 2.34 (95% CI = 1.02, 5.38) for perfluorooctane sulfonate (PFOS) exposure per natural log unit increase. After stratifying the estrogen receptor (ER) status and age group, we obtained a positive association for PFHxS and PFOS concentrations with respect to the risk of ER positive tumors for ≤50 years age group. In conclusion, we found that PFAS were associated with the BC risk of ER positive tumors in young Taiwanese women. Further studies are needed to follow and explore whether these associations are causal.	●	●							●	-		B	-
719	ヒト（発がん性）	Vieira, Verónica M; Hoffman, Kate; Shin, Hyeong-Moo; Weinberg, Janice M; Webster, Thomas F; Fletcher, Tony	Perfluorooctanoic acid exposure and cancer outcomes in a contaminated community: a geographic analysis	2019	Environ Health Perspect. 2013 Mar;121(3):318-23. doi: 10.1289/ehp.1205829. Epub 2013 Jan 8.	BACKGROUND: Perfluorooctanoic acid (PFOA) has been linked to cancer in occupational mortality studies and animal toxicologic research. OBJECTIVE: We investigated the relationship between PFOA exposure and cancer among residents living near the DuPont Teflon-manufacturing plant in Parkersburg, West Virginia (WV). METHODS: Our analyses included incident cases of 18 cancers diagnosed from 1996 through 2005 in five Ohio (OH) counties and eight WV counties. For analyses of each cancer outcome, controls comprised all other cancers in the study data set except kidney, pancreatic, testicular, and liver cancers, which have been associated with PFOA in animal or human studies. We applied logistic regression models to individual-level data to calculate adjusted odds ratios (AORs) and confidence intervals (CIs). For the combined analysis of OH and WV data, the exposure of interest was resident water district. Within OH, geocoded addresses were integrated with a PFOA exposure model to examine the relationship between cancer odds and categories of estimated PFOA serum. RESULTS: Our final data set included 7,869 OH cases and 17,238 WV cases. There was a positive association between kidney cancer and the very high and high serum exposure categories [AOR = 2.0 (95% CI: 1.0, 3.9) n = 9 and 2.0 (95% CI: 1.3, 3.2) n = 22, respectively] and a null association with the other exposure categories compared with the unexposed. The largest AOR was for testicular cancer with the very high exposure category [2.8 (95% CI: 0.8, 9.2) n = 6], but there was an inverse association with the lower exposure groups, and all estimates were imprecise because of small case numbers. CONCLUSIONS: Our results suggest that higher PFOA serum levels may be associated with testicular, kidney, prostate, and ovarian cancers and non-Hodgkin lymphoma. Strengths of this study include near-complete case ascertainment for state residents and well-characterized contrasts in predicted PFOA serum levels from six contaminated water supplies.	●	●		●		●			●	-		B	-
720	ヒト（発がん性）	Wielsøe, M.; Kern, P.; Bonefeld-Jørgensen, E. C.	Serum levels of environmental pollutants is a risk factor for breast cancer in Inuit: a case control study	2002	Environ Health. 2017 Jun 13;16(1):56. doi: 10.1186/s12940-017-0269-6.	BACKGROUND: Environmental Persistent Organic Pollutants (POPs) can alter the hormone homeostasis by mimicking, interfering or blocking the function of hormones; moreover POPs are hypothesized to modify the risk of breast cancer. The association between POPs and breast cancer has been widely studied but the conclusions are inconsistent. The present study examined the associations between serum levels of POPs and breast cancer with focus on the highly exposed Greenlandic Inuit population. METHODS: The study design was a case-control study of Inuit women from Greenland. The participants were asked to complete a questionnaire with information on reproductive history and lifestyle and to provide a blood sample. The sampling was carried out in two time periods (2000-2003 and 2011-2014). The serum levels were determined of 14 polychlorinated biphenyls (PCBs), 11 organochlorine pesticides (OCPs), 16 perfluoroalkyl acids (PFAAs), 1 polybrominated biphenyl (PBB), and 9 polybrominated diphenyl ethers (PBDEs). Independent samples t-test was used to compare differences between cases and controls and odds ratios (OR) adjusted for identified confounders were obtained using logistic regression. RESULTS: The study population included 77 breast cancer cases and 84 controls. The majority of the measured compounds declined significantly from 2000 - 2003 to 2011-2014. However, for the perfluorinated carboxylic acids (PFCAs) an increase was observed. The serum levels were significantly higher in cases compared to controls for the majority of the compounds, and after adjusting for age the difference was maintained for ∑OCP, dichlorodiphenyldichloroethylene (p,p'-DDE), ∑PFAA, ∑perfluorinated sulfonic acids (PFSA), perfluorohexane sulfonate (PFHxS), and perfluorooctane sulfonate (PFOS). For the lipophilic POPs, high serum levels (middel/highest vs. lowest tertile) of ∑PCB, ∑estrgoenicPCB, PCB99, PCB138, PCB153, PCB170, PCB170, and PCB183 was associated with breast cancer risk; for the amphiphilic PFAAs, high serum levels of ∑PFAA, ∑PFCA, ∑PFSA, perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), PFHxS, and PFOS were associated with breast cancer risk. CONCLUSION: Significant, positive associations between breast cancer risk and PCBs and PFAAs were observed. The associations indicate that environmental exposure to POPs can be a factor increasing the risk for breast cancer in Inuit perfluorinated carboxylic acids (PFCAs) an increase was observed. The serum levels were significantly higher in cases compared to controls for the majority of the compounds, and after adjusting for age the difference was maintained for ∑OCP, dichlorodiphenyldichloroethylene (p,p'-DDE), ∑PFAA, ∑perfluorinated sulfonic acids (PFSA), perfluorohexane sulfonate (PFHxS), and perfluorooctane sulfonate (PFOS). For the lipophilic POPs, high serum levels (middel/highest vs. lowest tertile) of ∑PCB, ∑estrgoenicPCB, PCB99, PCB138, PCB153, PCB170, PCB170, and PCB183 was associated with breast cancer risk; for the amphiphilic PFAAs, high serum levels of ∑PFAA, ∑PFCA, ∑PFSA, perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), PFHxS, and PFOS were associated with breast cancer risk.CONCLUSION: Significant, positive associations between breast cancer risk and PCBs and PFAAs were observed. The associations indicate that environmental exposure to POPs can be a factor increasing the risk for breast cancer in Inuit women. women.	●	●	●	●					●	-		B	-
721	ヒト（発がん性）	IARC (International Agency for Research on Cancer)	Some chemicals used as solvents and in polymer manufacture IARC monographs on the evaluation of carcinogenic risks to humans volume 110	2017	Available at http://monographs.iarc.fr/ENG/Monographs/vol110/mono110-01.pdf	No abstract available			●						評価書		D	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
722	ヒト（発がん性）	Consonni, Dario; Straif, Kurt; Symons, J Morel; Tomenson, John A; van Amelsvoort, Ludovic G P M; Sleeuwenhoek, Anne; Cherrie, John W; Bonetti, Paolo; Colombo, Ilaria; Farrar, David G; Bertazzi, Pier Alberto	Cancer risk among tetrafluoroethylene synthesis and polymerization workers	2013	Am J Epidemiol. 2013 Aug 1;178(3):350-8. doi: 10.1093/aje/kws588. Epub 2013 Jul 4.	Tetrafluoroethylene (TFE), a compound used for the production of fluorinated polymers including polytetrafluoroethylene, increases the incidence of liver and kidney cancers and leukemia in rats and mice. This is the first time the cancer risk in humans has been explored comprehensively in a cohort mortality study (1950-2008) that included all polytetrafluoroethylene production sites in Europe and North America at the time it was initiated. A job-exposure matrix (1950-2002) was developed for TFE and ammonium perfluoro-octanoate, a chemical used in the polymerization process. National reference rates were used to calculate standardized mortality ratios (SMRs) and 95% confidence intervals. Among 4,773 workers ever exposed to TFE, we found a lower rate of death from most causes, as well as increased risks for cancer of the liver (SMR = 1.27; 95% confidence interval: 0.55, 2.51; 8 deaths) and kidney (SMR = 1.44; 95% confidence interval: 0.69, 2.65; 10 deaths) and for leukemia (SMR = 1.48; 95% confidence interval: 0.77, 2.59; 12 deaths). A nonsignificant upward trend (P = 0.24) by cumulative exposure to TFE was observed for liver cancer. TFE and ammonium perfluoro-octanoate exposures were highly correlated, and therefore their separate effects could not be disentangled. This pattern of findings narrows the range of uncertainty on potential TFE carcinogenicity but cannot conclusively confirm or refute the hypothesis that TFE is carcinogenic to humans.				●						-		B	-
723	ヒト（発がん性）	Gilliland, F D; Mandel, J S	Mortality among employees of a perfluorooctanoic acid production plant	1993	J Occup Med. 1993 Sep;35(9):950-4. doi: 10.1097/00043764-199309000-00020.	Perfluorooctanoic acid (PFOA) has been found at low levels (10 to 100 parts per billion) in sera of the general population and at higher levels in occupationally exposed workers. Although PFOA has been reported to be a promoter of rodent hepatocarcinogenesis and to alter reproductive hormones in humans and rodents, there is little information on human health effects associated with PFOA exposure. The present study examined the relationship between PFOA and mortality using a retrospective cohort mortality design. The cohort consisted of 2788 male and 749 female workers employed between 1947 and 1983 at a plant that produced PFOA. The all-causes standardized mortality ratio was .75 (95% confidence interval [CI], .56 to .99) for women and .77 (95% CI, .69 to .86) for men. Among men the cardiovascular standardized mortality rate was .68 (95% CI, .58 to .80) and the all-gastrointestinal diseases was .57 (95% CI, .29 to .99). There was no significantly increased cause-specific standardized mortality ratio for either men or women. Ten years of employment in exposed jobs was associated with a 3.3-fold increase (95% CI, 1.02 to 10.6) in prostate cancer mortality compared to no employment in PFOA production. There were only six prostate cancer deaths overall and four among the exposed workers; thus, the results must be interpreted cautiously. If prostate cancer mortality is related to PFOA, PFOA may increase prostate cancer mortality by altering reproductive hormones in male workers.				●						-		B	-
724	ヒト（発がん性）	IARC.	Perfluorooctanoic acid (PFOA)	2017	IARC Monographs on the evaluation of carcinogenic risks to humans. Volume 110.	No abstract available				●					評価書		D	-
725	ヒト（発がん性）	Leonard RC.	Ammonium perfluorooctanoate: Phase II. Retrospective cohort mortality analyses related to a serum biomarker of exposure in a polymer production plant	2006	Wilmington, DE: E.I. du pont de Nemours and Company.	No abstract available				●					企業データ		D	-
726	ヒト（発がん性）	Ghisari, M; Long, M; Røge, DM; Olsen, J; Bonefeld-Jørgensen, EC	Polymorphism in xenobiotic and estrogen metabolizing genes, exposure to perfluorinated compounds and subsequent breast cancer risk: A nested case-control study in the Danish National Birth Cohort	2017	Environ Res. 2017 Apr;154:325-333. doi: 10.1016/j.envres.2017.01.020. Epub 2017 Feb 2.	In the present case-cohort study based on prospective data from Danish women, we aimed to estimate the main effect of polymorphisms in genes known to be involved in the steroid hormone metabolic pathway and xenobiotic metabolism on the risk of developing breast cancer. We also studied a possible effect measure modification between genotypes and levels of serum perfluoroalkylated substances (PFASs) on the risk to breast cancer. We have previously reported a weak association between serum PFASs levels and the risk of breast cancer for this study population of Danish pregnant nulliparous women as well as in a smaller case-control study of Greenlandic women. The study population consisted of 178 breast cancer cases and 233 controls (tabnulliparous and frequency matched on age) nested within the Danish National Birth Cohort (DNBC), which was established in 1996-2002. Blood samples were drawn at the time of enrollment (6-14 week of gestation). Serum levels of 10 perfluorocarboxylated acids (PFCAs), 5 perfluorosulfonated acids (PFSAs) and 1 sulfonamide (perfluorooctane-sulfonamide, PFOSA) were measured. Genotyping was conducted for CYP1A1 (Ile462Val; rs1048943), CYP1B1 (Leu432Val; rs1056836), COMT (Val158Met; rs4680), CYP17A1 (A1→ A2; rs743572); CYP19A1 (C→T; rs10046) by the TaqMan allelic discrimination method. In overall, no significant associations were found between the investigated polymorphisms and the risk of breast cancer in this study among Danish women. The previously found association between PFOSA and risk of breast cancer did vary between different genotypes, with significantly increased risk confined to homozygous carriers of the following alleles: COMT (Met), CYP17 (A1) and CYP19 (C). following alleles: COMT (Met), CYP17 (A1) and CYP19 (C). CONCLUSION: Our results indicate that polymorphisms in COMT, CYP17 and CYP19 which are involved in estrogen biosynthesis and metabolism can modulate the potential effects of PFOSA exposure on the development of breast cancer.				●						-		C	-
727	ヒト（発がん性）	U.S. EPA	Toxicological Review of Trichloroethylene (CASRN 79-01-6) in support of summary information on the Integrated Risk Information System (IRIS)	2011	Available at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0199tr/Chapter6_0199tr.pdf	No abstract available		●							EPA評価書？		D	-
728	ヒト（発がん性）	Olsen, G.W., Burlew, M.M., Hocking, B.B., Skratt, J.C., Burris, J.M. and Mandel, J.H.	An epidemiologic analysis of episodes of care of 3M Decatur chemical and film plant employees, 1993–1998	2001	Final Report May 18. [As cited in EFSA (2008)].	No abstract available					●				企業データ		D	-
729	ヒト（発がん性）	C8 Science Panel	C8 probable link reports (probable link evaluations for cancer and diabetes）	2012	Available at: www.c8sciencepanel.org/prob_link.html.	No abstract available						●			C8 science panel ウェブサイト公表資料。対象外とする		D	-
730	ヒト（発がん性）	IARC Working Group on the Evaluation of Carcinogenic Risks to Humans.	Some Chemicals Used as Solvents and in Polymer Manufacture	2017	Lyon (FR): International Agency for Research on Cancer.	This volume of the IARC Monographs provides evaluations of the carcinogenicity of perfluorooctanoic acid, tetrafluoroethylene, 1,2-dichloropropane, dichloromethane, and 1,3-propane sultone. Perfluorooctanoic acid is a fluorinated chemical that persists in the environment, having been detected in air, water, dust, and food. It is particularly important for the production of fluoropolymers such as polytetrafluoroethylene, which has a wide range of uses in industrial and consumer products, including non-stick coatings on cookware and waterproof clothing. Tetrafluoroethylene is a fluorinated monomer that is used mainly as an intermediate in the production of polytetrafluoroethylene. The chlorinated solvent 1,2-dichloropropane is used primarily as a production intermediate, but also in paint stripping and, until 2012, in printing-press cleaning in Japan. Dichloromethane is a chlorinated solvent that is used in paint stripping, aerosols, polycarbonate plastic and hydrofluorocarbon manufacture, metal and printing-press cleaning, and refrigerant production. Industrial use of the alkylating agent 1,3-propane sultone was largely discontinued in the 1960s, but it has been used recently in the manufacture of lithium batteries, and for chemical synthesis in the laboratory. Exposure to all five agents considered occurs in the general population as well as in different occupational settings. An IARC Monographs Working Group reviewed epidemiological evidence, animal bioassays, and mechanistic and other relevant data to reach conclusions as to the carcinogenic hazard to humans of environmental or occupational exposure to these agents.								●		評価書		A	-
731	ヒト（発がん性）	Science Advisory Board (SAB)	Review of EPA's Analyses to Support EPA's National Primary Drinking Water Reulemaking for PFAS	2022	Available at https://sab.epa.gov/ords/sab/f?p=100:18:16490947993:::RP,18:P18_ID:2601#report. Accessed 27 September 2022.	No abstract available								●	SAB評価書		D	-
732	ヒト（肝毒性）	Attanasio, R.	Sex differences in the association between perfluoroalkyl acids and liver function in US adolescents: Analyses of NHANES 2013-2016	2019	Environ Pollut. 2019 Nov;254(Pt B):113061. doi: 10.1016/j.envpol.2019.113061. Epub 2019 Aug 15.	Perfluoroalkyl acids (PFAAs) are persistent in the environment, highly bio-accumulative in the body, and likely hepatotoxic in humans. There is evidence of sex-specific physiological responses to PFAA exposure. However, epidemiological studies seldom stratify the analyses by sex. Given the high prevalence of liver disease in general population adolescents, this study was designed to determine whether or not there is association between exposure to PFAAs and biomarkers of liver function in adolescent participants of the 2013-2016 National Health and Nutrition Examination Survey, and whether or not such association is sex-specific. Multivariate linear regressions were performed to examine the association between single PFAAs [perfluorooctane sulfonic acid (PFOS); linear form of perfluorooctanoic acid (PFOA); perfluorohexane sulfonic acid (PFHxS); perfluorononanoic acid (PFNA)], and biomarkers of liver function - gamma glutamyltransferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin. Multivariate logistic regressions were performed to estimate adjusted odd ratios (aOR) of elevated ALT, AST and GGT. The study results show that, in females, there was a positive association of the highest PFOA quartile with increased ALT, AST and GGT, and the highest PFNA quartile with increased ALT and AST. Conversely, in male adolescents there was an association of the highest linear PFOA quartile with decreased ALT, and the highest PFNA quartile with ALT and AST. Females had higher odds of clinically-defined elevated ALT with increased PFOA (aOR = 1.79; 0.95 CI: 1.05, 3.04) or PFNA (aOR = 2.28; 0.95 CI: 1.08, 2.28), whereas males had decreased odds of clinically-defined elevated ALT with increased n-PFOA (aOR = 0.43; 0.95 CI: 0.20, 0.93) or PFNA (aOR = 0.5; 0.95 CI: 0.28, 0.89). In conclusion, there were sex differences in the association between serum PFAA levels and biomarkers of liver function. These results may provide support for analyzing sex-based adverse effects of PFAAs.	●	●								-	1	A	A

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献ランク①	文献ランク②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
733	ヒト（肝毒性）	Boone, L.; Meyer, D.; Cusick, P.; Ennulat, D.; Bolliger, A. P.; Everds, N.; Meador, V.; Elliott, G.; Honor, D.; Bounous, D.; Jordan, H.	Selection and interpretation of clinical pathology indicators of hepatic injury in preclinical studies [Review]	2005	Vet Clin Pathol。2005 Sep;34(3):182-8. doi: 10.1111/j.1939-165x.2005.tb00041.x.	This position paper delineates the expert recommendations of the Regulatory Affairs Committee of the American Society for Veterinary Clinical Pathology for the use of preclinical, clinical pathology endpoints in assessment of the potential for drug-induced hepatic injury in animals and humans. Development of these guidelines has been based on current recommendations in the relevant preclinical and human clinical trial literature; they are intended to provide a method for consistent and rigorous interpretation of liver-specific data for the identification of hepatic injury in preclinical studies and potential liability for hepatic injury in human patients.	●	●								-		D	C
734	ヒト（肝毒性）	Darrow, L. A.; Groth, A. C.; Winquist, A.; Shin, H. M.; Bartell, S. M.; Steenland, K.	Modeled perfluorooctanoic acid (PFOA) exposure and liver function in a mid-Ohio valley community	2016	Environ Health Perspect. 2016 Aug;124(8):1227-33. doi: 10.1289/ehp.1510391. Epub 2016 Mar 15.	BACKGROUND: Perfluorooctanoic acid (PFOA or C8) has hepatotoxic effects in animals. Cross-sectional epidemiologic studies suggest PFOA is associated with liver injury biomarkers.OBJECTIVES: We estimated associations between modeled historical PFOA exposures and liver injury biomarkers and medically validated liver disease.METHODS: Participants completed surveys during 2008-2011 reporting demographic, medical, and residential history information. Self-reported liver disease, including hepatitis, fatty liver, enlarged liver and cirrhosis, was validated with healthcare providers. Alanine aminotransferase (ALT), γ-glutamyltransferase (GGT) and direct bilirubin, markers of liver toxicity, were obtained from blood samples collected in the C8 Health Project (2005-2006). Historically modeled PFOA exposure, estimated using environmental fate and transport models and participant residential histories, was analyzed in relation to liver biomarkers (n = 30,723, including 1892 workers) and liver disease (n = 32,254, including 3713 workers).RESULTS: Modeled cumulative serum PFOA was positively associated with ALT levels (p for trend < 0.0001), indicating possible liver toxicity. An increase from the first to the fifth quintile of cumulative PFOA exposure was associated with a 0.06 increase in ALT levels (95% CI: 4, 8%) and a 0.16 increased odds of having above-normal ALT (95% CI: odds ratio: 1.02, 1.33%). There was no indication of association with either elevated direct bilirubin or GGT; however, PFOA was associated with decreased direct bilirubin. We observed no evidence of an effect of cumulative exposure (with or without a 10-year lag) on all liver disease (n = 647 cases), nor on enlarged liver, fatty liver, and cirrhosis only (n = 427 cases).CONCLUSION: Results are consistent with previous cross-sectional studies showing association between PFOA and ALT, a marker of hepatocellular damage. We did not observe evidence that PFOA increases the risk of clinically diagnosed liver disease.CITATION: Darrow LA, Groth AC, Winquist A, Shin HM, Bartell SM, Steenland K. 2016 Modeled perfluorooctanoic acid (PFOA) exposure and liver function in a Mid-Ohio Valley community.	●	●		●						-	1	A	B
735	ヒト（肝毒性）	Fan, H.; Ducatman, A.; Zhang, J.	Perfluorocarbons and Gilbert syndrome (phenotype) in the C8 Health Study Population	2014	Environ Res. 2014 Nov;135:70-5. doi: 10.1016/j.envres.2014.08.011. Epub 2014 Sep 28.	BACKGROUND: Gilbert syndrome (GS) is an inherited defect of bilirubin conjugation, most commonly caused by a gene mutation for the enzyme UGT1A. GS is known to affect the metabolism and excretion of drugs and xenobiotics. Perfluorocarbon compounds (PFCs) are bio-persistent environmental contaminants that affect metabolic regulation. In this study, we examined the associations of GS phenotype and serum PFCs in the C8 Health Study Population.MATERIALS AND METHODS: Using 2005-2006 data from a large PFC-exposure population survey, we compared serum PFCs concentrations between GS and non GS clinical phenotypes, in a cross sectional design, adjusting for standard risk factors, including age, BMI, smoking status, socioeconomic status and gender.RESULTS: Among 10 PFC compounds considered, only perfluorohexanoic acid (PFHxA) was seen at a significantly higher concentration in GS men and women.CONCLUSION: PFHxA exposure may be associated with GS. Our findings do not support increased exposure in GS for other PFCs.	●	●								-		B	C
736	ヒト（肝毒性）	Kang, H.; Lee, H. K.; Moon, H. B.; Kim, S.; Lee, J.; Ha, M.; Hong, S.; Kim, S.; Choi, K.	Perfluoroalkyl acids in serum of Korean children: Occurrences, related sources, and associated health outcomes	2018	Sci Total Environ. 2018 Dec 15;645:958-965. doi: 10.1016/j.scitotenv.2018.07.177. Epub 2018 Jul 20.	Perfluoroalkyl acids (PFAAs) have been widely used in human environment, and their exposure among general population has been frequently reported. However, extent of PFAAs exposure and their potential effects among children are not well characterized. In this study, children of between 3 and 18 years of age (n = 150) were recruited in Seoul and Gyeonggi, Korea, and the serum levels of 16 PFAAs along with lipids and thyroid hormones were measured. Questionnaire survey was conducted for dietary and behavioral characteristics of the children. Among the measured PFAAs, PFOA, PFNA, PFHxS, and PFOS were detected in all the samples, and PFUnDA and PFDA were detected in over 0.75 of the samples. PFOS was detected at the highest concentration with a median of 5.68 ng/mL. PFUnDA was detected at higher levels (median of 0.652 ng/mL) compared to those reported for children in USA. Serum PFAA levels were not different by sex among the children of <10 years of age, but in older children, those of boys are significantly higher than girls. Physiological characteristics like menstruation may explain lower PFAAs levels of the girls. In addition, breastmilk consumption, fish/shellfish consumption, non-stick frying pan use, and waterproof cloth use were identified as potential sources of PFAAs exposure. Serum PFUnDA level was positively associated with total cholesterol and low-density lipoprotein level of the children. PFNA was positively associated with free T4 level. High levels of PFUnDA among children and its association with serum lipids warrant replication and confirmation in other populations and/or supports by experimental studies.	●	●		●						-		B	B
737	ヒト（肝毒性）	Lin, Chien-Yu; Lin, Lian-Yu; Chiang, Chih-Kang; Wang, Wei-Jie; Su, Yi-Ning; Hung, Kuan-Yu; Chen, Pau-Chung	Investigation of the Associations Between Low-Dose Serum Perfluorinated Chemicals and Liver Enzymes in US Adults	2010	Am J Gastroenterol. 2010 Jun;105(6):1354-63. doi: 10.1038/ajg.2009.707. Epub 2009 Dec 15.	OBJECTIVES: Perfluorinated chemicals (PFCs) have been largely used for years in a variety of products worldwide. However, the toxic effect of PFCs on exposure to the liver in the general population has not yet been determined. METHODS: In this study, 2,216 adults (18 years of age or older) were recruited in a National Health and Nutrition Examination Survey (NHANES) in 1999-2000 and 2003-2004 to determine the relationship between serum level of PFCs and the levels of liver enzymes. The data were adjusted for all other confounding variants. RESULTS: After performing mathematical analysis, we determined when serum log-perfluorooctanoic acid (PFOA) increases in one unit, the serum alanine aminotransferase (ALT) concentration (U/l) increases by 1.86 units (95% confidence interval (CI), 1.24-2.48; P=0.005), and the serum log-gamma-glutamyltransferase (GGT) concentration (U/l) is 0.08 unit higher (95% CI, 0.05-0.11; P=0.019). The association between PFOA and liver enzymes was more evident in obese subjects, as well as subjects with insulin resistance and/or metabolic syndromes. When dividing the serum PFOA into quartiles in the fully adjusted models in subjects with a body mass index>or=30 kg/m2, the ALT level trend across the serum PFOA quartiles was significant (P=0.003). CONCLUSIONS: On the basis of these data, we conclude that a higher serum concentration of PFOA may cause liver enzymes to increase abnormally in the general population, particularly in obese individuals. Further studies are warranted to clarify the casual relationship between PFCs and these liver enzymes.	●	●	●	●		●				-	1	A	A
738	ヒト（肝毒性）	Olsen, GW; Burris, JM; Burlew, MM; Mandel, JH.	3M final report: an epidemiologic investigation of plasma cholecystokinin, hepatic function and serum perfluorooctanoic acid levels in production workers	1998	(U.S. Environmental Protection Agency Administrative Record 226-0476). 3M Company.	No abstract available	●	●								企業データ		D	D
739	ヒト（肝毒性）	Olsen, Geary W; Burris, Jean M; Burlew, Michele M; Mandel, Jeffrey H	Epidemiologic assessment of worker serum perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) concentrations and medical surveillance examinations	2003	J Occup Environ Med. 2003 Mar;45(3):260-70. doi: 10.1097/01.jom.0000052958.59271.10.	Perfluorooctanesulfonyl fluoride (POSF, C8F17SO2F) is used to create applications for surfactants and paper, packaging, and surface (e.g., carpets, textiles) protectants. Such POSF-based products or their residuals may degrade or metabolize to PFOS (C8F17SO3-). PFOS concentrates in liver and serum and results in hypolipidemia as an early effect of cumulative dosages. Male and female employees of two perfluorooctanyl-manufacturing locations (Antwerp, Belgium and Decatur, Alabama) participated in a periodic medical surveillance program that included hematology, clinical chemistry, thyroid hormone, and urinalysis testing. Serum concentrations of PFOS and perfluorooctanoate (PFOA, C7F15CO2-, used as a fluoropolymer emulsifier) were measured via mass spectrometry methods. The mean serum PFOS and PFOA concentrations for 263 Decatur employees were 1.32 parts per million (ppm; geometric mean 0.91, range 0.06-10.06 ppm) and 1.78 ppm (geometric mean 1.13, range 0.04-12.70 ppm), respectively. Mean concentrations were approximately 50% lower among 255 Antwerp workers. Adjusting for potential confounding factors, there were no substantial changes in hematological, lipid, hepatic, thyroid, or urinary parameters consistent with the known toxicological effects of PFOS or PFOA in cross-sectional or longitudinal analyses of the workers' measured serum fluorochemical concentrations.	●	●		●		●	●			-		B	B
740	ヒト（肝毒性）	Olsen, G. W.; Ehresman, D. J.; Buehrer, B. D.; Gibson, B. A.; Butenhoff, J. L.; Zobel, L. R.	Longitudinal assessment of lipid and hepatic clinical parameters in workers involved with the demolition of perfluoroalkyl manufacturing facilities	2012	J Occup Environ Med. 2012 Aug;54(8):974-83. doi: 10.1097/JOM.0b013e31825461d2.	OBJECTIVE: To examine in a longitudinal occupational assessment whether changes in serum concentrations of perfluorooctanoic acid (PFOA) and perfluorooctanesulfonate (PFOS) are associated with changes in non-high-density lipoprotein (HDL) cholesterol.METHODS: Baseline and end-of-project PFOA, PFOS, lipid, and hepatic clinical chemistries were measured in 204 workers involved with the demolition of former perfluoroalkyl manufacturing facilities. Analyses were restricted to the 179 workers who did not take lipid-lowering medications. Two thirds had baseline PFOA and PFOS levels similar to the general population.RESULTS: The change in non-HDL cholesterol was not associated with the changes in PFOA or PFOS. An increase in HDL was associated with an increase in PFOA, although the magnitude was small. This increase in HDL resulted in a decrease in the total cholesterol/HDL ratio.CONCLUSION: Adverse associations were not observed between changes in PFOA, PFOS, non-HDL cholesterol, HDL, and hepatic clinical chemistries.		●		●	●	●	●			-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報抽出対象	文献ランク①	文献ランク②
741	ヒト（肝毒性）	Olsen, Geary W; Zobel, Larry R	Assessment of lipid, hepatic, and thyroid parameters with serum perfluorooctanoate (PFOA) concentrations in fluorochemical production workers	2007	Int Arch Occup Environ Health. 2007 Nov;81(2):231-46. doi: 10.1007/s00420-007-0213-0. Epub 2007 Jun 29.	OBJECTIVES: Perfluorooctanoic acid (PFOA) results in peroxisome proliferator mediated effects in rats and mice resulting in hypolipidemia but not in monkeys. Counterintuitive modestly positive associations between PFOA and cholesterol levels in production workers have been inconsistently reported. The purpose of this assessment was to examine this association in male workers who manufactured or used PFOA at three facilities. METHODS: Subjects were male employee voluntary participants of a fluorochemical medical surveillance program who provided blood samples for serum measurement of PFOA (perfluorooctanoate) and various lipid, hepatic, and thyroid parameters. Statistical analyses included multiple and logistic regression and analysis of covariance. RESULTS: A total of 506 employees, who did not take cholesterol-lowering medications (93% of all male participants), were analyzed. Serum PFOA concentrations ranged from 0.007 to 92.03 microg/ml [arithmetic mean 2.21 microg/ml (95% confidence interval 1.66-2.77), median 1.10 microg/ml]. Adjusted for age, body mass index, and alcohol usage in regression analyses, PFOA was not statistically significantly (P>0.05) associated with total cholesterol or low-density lipoproteins (LDL). High-density lipoproteins (HDL) were significantly negatively (P<0.01) associated with PFOA for the three facilities combined but not by individual sites, indicating the overall result was likely a consequence of residual confounding due to different demographic profiles at these sites. Serum triglycerides were significantly positively associated with PFOA but not consistently by locations. There were no statistically significant associations observed between PFOA and hepatic enzymes at the three facilities combined although some modest positive associations were observed between PFOA and hepatic enzymes at one of the three facilities. Analyses of all locations showed no associations with TSH or T4 and PFOA. A negative association was observed for free T4 and positive association for T3; however, the findings were well within these assays' normal reference ranges. CONCLUSION: There was no evidence that employees' serum PFOA concentrations were associated with total cholesterol or LDL. A negative association with HDL was explained by demographic differences across the three locations. Several explanations are offered for the inconsistent triglyceride associations with PFOA including both methodological as well as biological possibilities.	●	●		●		●	●		●	-		B	B
742	ヒト（肝毒性）	Bassler, John; Ducatman, Alan; Elliott, Meenal; Wen, Sijin; Wahlang, Banrida; Barnett, John; Cave, Matthew C	Environmental perfluoroalkyl acid exposures are associated with liver disease characterized by apoptosis and altered serum adipocytokines	2019	Environ Pollut. 2019 Apr;247:1055-1063. doi: 10.1016/j.envpol.2019.01.064. Epub 2019 Jan 18.	Exposures to perfluoroalkyl substances (PFAS) including perfluoroalkyl acids (PFAAs) are associated with increased liver enzymes in cohort studies including the C8 Health Study. In animal models, PFAAs disrupt hepatic lipid metabolism and induce apoptosis to cause nonalcoholic fatty liver disease (NAFLD). PFAAs are immunotoxic and inhibit pro-inflammatory cytokine release from stimulated leukocytes in vitro. This cross-sectional study tests the hypothesis that environmental PFAAs are associated with increased hepatocyte apoptosis and decreased pro-inflammatory cytokines in serum. Biomarkers previously associated with PFAS exposures and/or NAFLD were evaluated as secondary endpoints. Two hundred adult C8 Health Study participants were included. Measured serum biomarkers included: perfluorohexane sulfonate (PFHxS); perfluorooctanoic acid (PFOA); perfluorooctane sulfonate (PFOS); perfluorononanoic acid (PFNA); cytokeratin 18 M30 (CK18 M30, hepatocyte apoptosis); adipocytokines; insulin; and cleaved complement 3 (C3a). Confounder-adjusted linear regression models determined associations between PFAS and disease biomarkers with cut-offs determined by classification and regression tree analysis. CK18 M30 was positively associated with PFHxS (β = 0.889, p = 0.042); PFOA (β = 2.1, p = 0.005); and PFNA (β = 0.567, p = 0.03). Tumor necrosis factor α (TNFα) was inversely associated with PFHxS (β = -0.799, p = 0.001); PFOA (β = - 1.242, p = 0.001); and PFOS (β = -0.704, p < 0.001). Interleukin 8 was inversely associated with PFOS and PFNA. PFAAs were also associated with sexually dimorphic adipocytokine and C3a responses. Overall, PFAA exposures were associated with the novel combination of increased biomarkers of hepatocyte apoptosis and decreased serum TNFα. These data support previous findings from cohorts and experimental systems that PFAAs may cause liver injury while downregulated some aspects of the immune response. Further studies of PFAAs in NAFLD are warranted and should evaluate sex differences.			●							-	1	A	A
743	ヒト（肝毒性）	Anderson-Mahoney, Pamela; Kotlerman, Jenny; Takhar, Harpreet; Gray, David; Dahlgren, James	Self-reported health effects among community residents exposed to perfluorooctanoate	2008	New Solut. 2008;18(2):129-43. doi: 10.2190/NS.18.2.d.	Serious health effects due to perfluorooctanoate (PFOA) exposure are suspected. The aim of this study was to evaluate the health status of nearby residents, with prolonged exposure to PFOA in their drinking water. A population of 566 white residents who were plaintiffs or potential plaintiffs in a lawsuit was evaluated by questionnaire for health history and symptoms. Standardized Prevalence Ratios were estimated using National Health and Examination Survey (NHANES) data files for comparison rates. The exposed subjects reported statistically significant greater prevalence of angina, myocardial infarction, and stroke (SPR=8.07, 95% C.I.=6.54-9.95; SPR=1.91, 95% C.I.=1.40-2.62, and SPR=2.17, 95% C.I.=1.47-3.21, respectively), chronic bronchitis, shortness of breath on stairs, asthma (SPR=3.60, 95% C.I.=2.92-4.44; SPR=2.05, 95% C.I.=1.70-2.46; SPR=1.82, 95% C.I.=1.47-2.25, respectively), and other serious health problems. The increased prevalence of adverse health effects may be due to PFOA. Further study is needed.				●						-		C	C
744	ヒト（肝毒性）	Butenhoff, John L; Gaylor, David W; Moore, John A; Olsen, Geary W; Rodricks, Joseph; Mandel, Jeffrey H; Zobel, Larry R	Characterization of risk for general population exposure to perfluorooctanoate	2004	Regul Toxicol Pharmacol. 2004 Jun;39(3):363-80. doi: 10.1016/j.yrtph.2004.03.003.	Perfluorooctanoate (PFOA), an environmentally and metabolically stable perfluorinated carboxylic acid, has been detected in the serum of children, adults and the elderly from the United States with the upper bound of the 95th percentile estimate in the range of 0.011-0.014 microg/mL (ppm). In this risk characterization, margins of exposure (MOE), which can provide a realistic perspective on potential for human risk, were determined by comparison of general population serum PFOA concentrations with serum concentrations from toxicological studies that are associated with the lower 95% confidence limit of a modeled 10 percent response or incidence level (LBMIC(10)) using USEPA BMDS software. The LBMIC(10) was estimated using surrogate data from other studies or pharmacokinetic relationships if serum PFOA data were not available. Modeled dose-responses (with resulting LBMIC(10) values) included post-natal effects in rats (29 microg/mL), liver-weight increase (23 microg/mL), and body-weight change (60 microg/mL) in rats and monkeys, and incidence of Leydig cell adenoma (125 microg/mL) in rats. MOE values based on the upper bound 95th percentile population serum PFOA concentration were large, ranging from 1600 (liver-weight increase) to 8900 (Leydig cell adenoma). These MOE values represent substantial protection of children, adults, and the elderly.				●						-		C	B
745	ヒト（肝毒性）	Carr Caroline K; Watkins, Andrew M; Wolf, Cynthia J; Abbott, Barbara D; Lau, Christopher; Gennings, Chris	Testing for departures from additivity in mixtures of perfluoroalkyl acids (PFAAs)	2013	Toxicology. 2013 Apr 5;306:169-75. doi: 10.1016/j.tox.2013.02.016. Epub 2013 Mar 5.	This study is a follow-up to a paper by Carr et al. that determined a design structure to optimally test for departures from additivity in a fixed ratio mixture of four perfluoroalkyl acids (PFAAs) using an in vitro transiently-transfected COS-1 PPARα reporter model with a mixing ratio that is based on average serum levels in NHANES subjects. Availability of information regarding potential for additivity of PFAAs in mixtures is critically important for risk assessors who are concerned with the ability of the compounds to affect human health and impact ecological systems. It is clear that exposures are not to single compounds, but to mixtures of the PFAAs. This paper presents the results from the data collected using the design from Carr et al. along with subsequent analyses that were performed to classify the relationships among mixtures of PFAAs. A non-linear logistic additivity model was employed to predict relative luciferase units (RLU), an indicator of PPARα activation. The results indicated a less than additive relationship among the four PFAAs. To determine if the possible "antagonism" is from the competition among or between carboxylates and sulfonates, four different binary mixtures were also studied. There was a less than additive relationship in all four binary mixtures. These findings are generally similar to two other reports of interfering interactions between PFAAs in mixtures. The most conservative interpretation for our data would be an assumption of additivity (and lack of a greater than additive interaction), with a potential for antagonistic interactions.				●	●	●				-		D	B
746	ヒト（肝毒性）	Costa, G.	Report on the meeting held on Friday 20th and Saturday 21st 2004 at the Inn at Montchanin Village (Wilmington, USA) with 3M and DuPont delegations	2004	DuPont. Submitted to the U.S. Environmental Protection Agency. AR226-1866.	No abstract available				●						企業データ		D	D
747	ヒト（肝毒性）	Costa, Giovanni; Sartori, Samantha; Consonni, Dario	Thirty years of medical surveillance in perfluooctanoic acid production workers	2009	J Occup Environ Med. 2009 Mar;51(3):364-72. doi: 10.1097/JOM.0b013e3181965d80.	OBJECTIVE: To report health outcomes of 30 years (1978-2007) of medical surveillance of workers engaged in a perfluooctanoic acid (PFOA) production plant. METHODS: Fifty-three males workers (20 to 63 years) were submitted every year to medical examination and blood chemical chemistry tests, and serum PFOA dosage. RESULTS: In the latest survey PFOA serum levels ranged from 0.20 to 47.04 microg/mL in currently exposed workers, and from 0.53 to 18.66 microg/mL in those formerly exposed. No clinical evidence of any specific trouble or disease has been recorded over the 30 years, and all the biochemical parameters, including liver, kidney and hormonal functions, turned out to be within the reference ranges, but a significant association of total cholesterol and uric acid with and PFOA serum level was evidenced. CONCLUSIONS: A probable interference of PFOA on intermediate metabolism deserves further investigations.		●		●		●	●			-		C	B
748	ヒト（肝毒性）	Deb, Subrata; Puthanveetil, Prasanth; Sakharkar, Prashant	A population-based cross-sectional study of the association between liver enzymes and lipid levels	2018	Int J Hepatol. 2018 Jun 3;2018:1286170. doi: 10.1155/2018/1286170. eCollection 2018.	BACKGROUND: To examine the association between low-density lipoprotein (LDL) and high-density lipoprotein (HDL) levels and liver enzyme functions. METHODS: The National Health and Nutrition Examination Survey (NHANES) data from 1999 to 2012 was used to examine the association between liver enzymes and lipid levels amongst adults in the United States. RESULTS: Sixteen percent adults had ALT > 40 U/L, 11% had AST > 40 U/L, and 96% had ALP > 120 U/L. Age, gender, and race/ethnicity showed significant association with LDL, HDL, and triglycerides levels. LDL greater than borderline high was associated with little over two times higher odds of elevated ALT (OR: 2.33, 95% CI: 2.17, 2.53, p ≤ 0.001) and AST (OR: 2.79, 95% CI: 2.55, 3.06, p ≤ 0.001). High HDL was associated with 50% higher odds for elevated ALT (OR: 1.51, 95% CI: 1.39, 1.64, p ≤ 0.001) and over two-and-half fold elevated AST (OR: 2.77, 95% CI: 2.47, 3.11, p ≤ 0.001). LDL-C, HDL-C, and triglycerides were found to be good predictor of elevated ALT, AST, and ALP levels. Similarly, old age and female gender were significant predictor of elevated ALT and AST (p ≤ 0.001). CONCLUSIONS: Underlying hepatic pathophysiology from dyslipidemia deserves further exploration due to its potential effects on hepatic drug metabolism/detoxification.				●						-		C	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
749	ヒト（肝毒性）	Emmett, Edward Anthony; Zhang, Hong; Shofer, Frances Susan; Freeman, David; Rodway, Nancy Virginia; Desai, Chintan; Shaw, Leslie Michael	Community exposure to perfluorooctanoate: Relationships between serum levels and certain health parameters	2006	J Occup Environ Med. 2006 Aug;48(8):771-9. doi: 10.1097/01.jom.0000233380.13087.37.	OBJECTIVE: The objective of this study was to determine whether certain biomarkers of toxicity and/or a past diagnosis of liver or thyroid disease were associated with serum perfluorooctanoate concentrations (PFOA) in a community with longstanding environmental exposure to PFOA. METHODS: Serum (PFOA), hematologic and biochemical biomarkers, and a questionnaire were administered to 371 residents selected by stratified random sampling and a lottery among volunteers. Median PFOA was 354 ng/mL (interquartile range, 181-571 ng/mL). RESULTS: No significant positive relationships between serum (PFOA) and liver or renal function tests, cholesterol, thyroid-stimulating hormone, or with red cell indices, white cell, or platelet counts. Mean serum (PFOA) was not increased in those with a history of liver or thyroid disease. CONCLUSIONS: No toxicity from PFOA was demonstrated using the measured end points; other end points need to be addressed.				●		●	●				-		C	B
750	ヒト（肝毒性）	Eriksen, Kirsten T; Raaschou-Nielsen, Ole; McLaughlin, Joseph K; Lipworth, Loren; Tjønneland, Anne; Overvad, Kim; Sørensen, Mette	Association between plasma PFOA and PFOS levels and total cholesterol in a middle-aged Danish population	2013	PLoS One. 2013;8(2):e56969. doi: 10.1371/journal.pone.0056969. Epub 2013 Feb 18.	Perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) are used in a variety of consumer products and have been detected worldwide in human blood. Recent studies mainly of highly exposed populations have indicated that PFOA and PFOS may affect serum cholesterol levels, but the magnitude of the effect may be inconsistent across exposure levels. The aim of the present cross-sectional study was to investigate the association between plasma PFOA and PFOS and total cholesterol in a general, middle-aged Danish population. The study population comprised 753 individuals (663 men and 90 women), 50-65 years of age, nested within a Danish cohort of 57,053 participants. Blood samples were taken from all cohort members at enrolment (1993-1997) and stored in a biobank at -150°C. Plasma levels of PFOA and PFOS and serum levels of total cholesterol were measured. The associations between plasma PFOA and PFOS levels and total cholesterol levels were analysed by generalized linear models, both crude and adjusted for potential confounders. We observed statistically significant positive associations between both perfluorinated compounds and total cholesterol, e.g. a 4.4 [95% CI = 1.1-7.8] higher concentration of total cholesterol (mg/dL) per interquartile range of PFOA plasma level. Sex and prevalent diabetes appeared to modify the association between PFOA and PFOS, respectively, and cholesterol. In conclusion, this study indicated positive associations between plasma PFOA and PFOS levels and total cholesterol in a middle-aged Danish population, although whether the observed pattern of results reflects a causal association is unclear.				●			●				-	1	B	A
751	ヒト（肝毒性）	Fitz-Simon, Nicola; Fletcher, Tony; Luster, Michael I; Steenland, Kyle; Calafat, Antonia M; Kato, Kayoko; Armstrong, Ben	Reductions in serum lipids with a 4-year decline in serum perfluorooctanoic acid and perfluorooctanesulfonic acid	2013	Epidemiology. 2013 Jul;24(4):569-76. doi: 10.1097/EDE.0b013e31829443ee.	BACKGROUND: Several epidemiological cross-sectional studies have found positive associations between serum concentrations of lipids and perfluorooctanoic acid (PFOA, or C8). A longitudinal study should be less susceptible to biases from uncontrolled confounding or reverse causality. METHODS: We investigated the association between within-individual changes in serum PFOA and perfluorooctanesulfonic acid (PFOS) and changes in serum lipid levels (low-density lipoprotein [LDL] cholesterol, high-density lipoprotein cholesterol, total cholesterol, and triglycerides) over a 4.4-year period. The study population consisted of 560 adults living in parts of Ohio and West Virginia where public drinking water had been contaminated with PFOA. They had participated in a cross-sectional study in 2005-2006, and were followed up in 2010, by which time exposure to PFOA had been substantially reduced. RESULTS: Overall serum concentrations of PFOA and PFOS fell by half from initial geometric means of 74.8 and 18.5 ng/mL, respectively, with little corresponding change in LDL cholesterol (mean increase 1.8%, standard deviation 26.6%). However, there was a tendency for people with greater declines in serum PFOA or PFOS to have greater LDL decrease. For a person whose serum PFOA fell by half, the predicted fall in LDL cholesterol was 3.6% (95% confidence interval = 1.5-5.7%). The association with a decline in PFOS was even stronger, with a 5% decrease in LDL (2.5-7.4%). CONCLUSIONS: Our findings from this longitudinal study support previous evidence from cross-sectional studies of positive associations between PFOA and PFOS in serum and LDL cholesterol.				●	●	●	●				-		B	C
752	ヒト（肝毒性）	Frisbee, Stephanie J; Shankar, Anoop; Knox, Sarah S; Steenland, Kyle; Savitz, David A; Fletcher, Tony; Ducatman, Alan M	Perfluorooctanoic acid, perfluorooctanesulfonate, and serum lipids in children and adolescents: Results from the C8 Health Project	2010	Arch Pediatr Adolesc Med. 2010 Sep;164(9):860-9. doi: 10.1001/archpediatrics.2010.163.	BACKGROUND: Perfluorooctanoic acid (PFOA) and perfluorooctanesulfonate (PFOS) are man-made compounds with widespread presence in human sera. In previous occupational and adult studies, PFOA and PFOS were positively associated with serum lipid levels. OBJECTIVE: To interrogate associations between PFOA and PFOS and serum lipids in children and adolescents. DESIGN: Cross-sectional community-based study. SETTING: Mid-Ohio River Valley. PARTICIPANTS: A total of 12 476 children and adolescents included in the C8 Health Project, which resulted from the pretrial settlement of a class action lawsuit pursuant to PFOA contamination of the drinking water supply. MAIN OUTCOME MEASURES: Serum lipids (total, high-density lipoprotein [HDL-C], and low-density lipoprotein [LDL-C] cholesterol and fasting triglycerides). RESULTS: Mean (SD) serum PFOA and PFOS concentrations were 69.2 (111.9) ng/mL and 22.7 (12.6) ng/mL, respectively. In linear regression after adjustment for covariables, PFOA was significantly associated with increased total cholesterol and LDL-C, and PFOS was significantly associated with increased total cholesterol, HDL-C, and LDL-C. Using general linear model analysis of covariance, between the first and fifth quintiles of PFOA there was a 4.6-mg/dL and a 3.8-mg/dL increase in the adjusted mean levels of total cholesterol and LDL-C levels, respectively, and an 8.5-mg/dL and a 5.8-mg/dL increase in the adjusted mean levels of total cholesterol and LDL-C, respectively, between the first and fifth quintiles of PFOS. Increases were 10 mg/dL for some age- and sex-group strata. Observed effects were nonlinear, with larger increases in total cholesterol and LDL-C levels occurring at the lowest range, particularly of PFOA. CONCLUSION: Although the epidemiologic and cross-sectional natures of this study limit causal inferences, the consistently observed associations between increasing PFOA and PFOS and elevated total cholesterol and LDL-C levels warrant further study.				●	●	●	●				-		B	B
753	ヒト（肝毒性）	Fu, Yaning; Wang, Tieyu; Wang, Pei; Fu, Quanliang; Lu, Yonglong	Effects of age, gender and region on serum concentrations of perfluorinated compounds in general population of Henan, China	2014	Chemosphere. 2014 Sep;110:104-10. doi: 10.1016/j.chemosphere.2014.02.020. Epub 2014 Mar 13.	133 Serum samples collected from Henan donors aged from 0 to 88years were analyzed for 12 perfluorinated compounds (PFCs). Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) accounted for 69.19% of the total PFCs in serum samples, with a median concentration of 1.43 and 1.47ngmL(-)(1), respectively. Other PFCs were detected at much lower concentrations, with median concentrations ranging from 0.03 to 0.37ngmL(-)(1). PFOA and PFOS were positively correlated (r=0.219) in serum samples, indicating that they may have common exposure pathways. For all donors (0-88years), significant increases in PFOA (r=0.239, p<0.01), perfluorononanoic acid (PFNA) (r=0.185, p<0.05) and PFOS (r=0.175, p<0.05) concentrations over age were found. Median concentrations of PFOA, PFNA, perfluorodecanoic acid (PFDA), and PFOS were higher in males than in females. Higher PFOA concentrations were found in urban populations than in rural populations. Since PFCs exposure in general population is prevalent, further studies are needed to explore its possible impacts on epidemiological factors.				●							-		C	C
754	ヒト（肝毒性）	Geiger, Sarah Dee; Xiao, Jie; Ducatman, Alan; Frisbee, Stephanie; Innes, Kim; Shankar, Anoop	The association between PFOA, PFOS and serum lipid levels in adolescents	2021	Chemosphere. 2014 Mar;98:78-83. doi: 10.1016/j.chemosphere.2013.10.005. Epub 2013 Nov 13.	INTRODUCTION: Dyslipidemia in children is associated with accelerated atherosclerosis and earlier cardiovascular disease development. Environmental exposure to perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) have been shown to be associated with dyslipidemia in adults. However, there are few general population studies examining this association in children or adolescents. In this context, we examined the association between serum PFOA and PFOS levels and dyslipidemia in a nationally representative sample of US adolescents. METHODS: A cross-sectional study was performed on 815 participants ⩽18 years of age from the National Health and Nutrition Examination Survey 1999-2008. The main outcome was dyslipidemia, defined as total cholesterol >170 mg/dL, low-density lipoprotein cholesterol (LDL-C) >110 mg/dL, high-density lipoprotein cholesterol (HDL-C) <40 mg/dL or triglycerides >150 mg/dL. RESULTS: We found that serum PFOA and PFOS were positively associated with high total cholesterol and LDL-C, independent of age, sex, race-ethnicity, body mass index, annual household income, physical activity and serum cotinine levels. Compared to subjects in quartile 1 (referent), the multivariable-adjusted odds ratio (95% confidence interval) for high total cholesterol among children in quartile 4 was 1.16 (1.05-2.12) for PFOA and 1.53 (1.11-1.64) for PFOS. PFOA and PFOS were not significantly associated with abnormal HDL-C and triglyceride levels. DISCUSSION: Our findings indicate that serum PFOA and PFOS are significantly associated with dyslipidemia in adolescents, even at the lower "background" exposure levels of the US general population.				●			●				-	1	B	A
755	ヒト（肝毒性）	Gilliland FD.	Fluorocarbons and human health: Studies in an occupational cohort: A thesis	2020	University of Minnesota, 29-229.	No abstract available				●								D	D
756	ヒト（肝毒性）	Gilliland, F D; Mandel, J S	Serum perfluorooctanoic acid and hepatic enzymes, lipoproteins, and cholesterol: A study of occupationally exposed men	2018	Am J Ind Med. 1996 May;29(5):560-8. doi: 10.1002/(SICI)1097-0274(199605)29:5<560::AID-AJIM17>3.0.CO;2-Z.	Perfluorooctanoic acid (PFOA) produces marked hepatic effects, including hepatomegaly, focal hepatocyte necrosis, hypolipidemia, and alteration of hepatic lipid metabolism in a number of animal species. In rodents, PFOA is a peroxisome proliferator, an inducer of members of the cytochrome P450 superfamily and other enzymes involved in xenobiotic metabolism, an uncoupler of oxidative phosphorylation, and may not be a cancer promoter. Although PFOA is the major organofluorine compound found in humans, little information is available concerning human responses to PFOA exposure. This study of 115 occupationally exposed workers examined the cross-sectional associations between PFOA and hepatic enzymes, lipoproteins, and cholesterol. The findings indicate that there is no significant clinical hepatic toxicity at the PFOA levels observed in this study. PFOA may modulate the previously described hepatic responses to obesity and xenobiotics.				●			●				-		C	C
757	ヒト（肝毒性）	Grice, Mira M; Alexander, Bruce H; Hoffbeck, Richard; Kampa, Diane M	Self-reported medical conditions in perfluorooctanesulfonyl fluoride manufacturing workers	2007	J Occup Environ Med. 2007 Jul;49(7):722-9. doi: 10.1097/JOM.0b013e3180582043.	OBJECTIVE: To evaluate whether some cancers, other conditions, and pregnancy outcomes were related to occupational perfluorooctane sulfonate (PFOS) exposure. METHODS: We surveyed current and former employees of a perfluorooctanesulfonyl fluoride production facility, using a self-administered questionnaire to ascertain several cancers and health conditions. Female cohort members also completed a brief pregnancy history. We requested medical records to validate reported melanoma, breast, prostate, and colon cancers. PFOS exposure was estimated based on a job exposure matrix up to the year of the diagnosis of the condition. RESULTS: Of the 1,895 eligible participants, 1,400 questionnaires were returned. No association was observed between working in a PFOS-exposed job and the risk of any of the surveyed conditions. CONCLUSION: We observed no association between working in a PFOS-exposed job and several cancers, common health conditions, and birth weight.				●			●				-		C	B
758	ヒト（肝毒性）	Kim WR, Flamm SL, Di Bisceglie AM, et al.	Serum activity of alanine aminotransferase (ALT) as an indicator of health and disease	2014	Hepatology. 2008 Apr;47(4):1363-70. doi: 10.1002/hep.22109.	No abstract available				●								D	D

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
759	ヒト（肝毒性）	Mundt, Diane J; Mundt, Kenneth A; Luippold, Rose S; Schmidt, Michael D; Farr, Craig H	Clinical epidemiological study of employees exposed to surfactant blend containing perfluorononanoic acid	2007	Occup Environ Med. 2007 Sep;64(9):589-94. doi: 10.1136/oem.2007.032664. Epub 2007 Apr 4.	INTRODUCTION: An epidemiological study was conducted of a perfluorononanoic acid (PFNA) surfactant blend, to investigate whether clinical differences were apparent between employees who were potentially exposed to the surfactant and those who were not exposed. The surfactant blend, which is related to other previously studied perfluorinated materials, is used in the production of some high-performance polymers. METHODS: All 630 individuals employed at a polymer production facility using PFNA (CAS No 72968-38-8) at any time between 1 January 1989 and 1 July 2003 were included in the cohort. Plausibly related laboratory test results were abstracted from annual medical examination records, including liver enzyme function and blood lipids. Detailed work histories, available for all employees, provided the basis for determining exposure category. Thirty two clinical parameters were evaluated by exposure level at five points in time, determined to reflect changes in possible exposure intensity, as well as greatest number of records available. Annual cross-sectional analyses and longitudinal analyses that accounted for multiple measurements per person were conducted separately for men and women, by exposure groups. RESULTS: Differences by exposure group for all laboratory measures, adjusted for age and body mass index, were small and not clinically significant. Although some statistically significant pair-wise differences were observed, these observations were not consistent between men and women, or over the five analysis windows. For the seven outcome variables (liver enzymes and blood lipids) examined in separate longitudinal models, no significant increase or decrease was observed by unit increase in cumulative exposure intensity score. CONCLUSION: This is the first epidemiological study investigating the possible health effects in humans associated with exposure to PFNA blend. Based on laboratory measures assessed over more than a decade, no adverse clinical effects were detected from occupational exposure to PFNA blend.				●						-		C	C
760	ヒト（肝毒性）	Olsen, Geary W; Burlew, Michele M; Marshall, Julia C; Burris, Jean M; Mandel, Jeffrey H	Analysis of episodes of care in a perfluorooctanesulfonyl fluoride production facility	2013	J Occup Environ Med. 2004 Aug;46(8):837-46. doi: 10.1097/01.jom.0000135546.70469.87.	The observed to expected episodes of care experience of 652 employees at a fluorochemical (perfluorooctanesulfonyl fluoride) production facility was compared with 659 film plant (nonfluorochemical) employees at the same site (Decatur, AL). Episodes of care were defined by a hierarchical analysis of health claims data from 1993 through 1998. The age- and sex-adjusted expected number of episodes of care was calculated from the company's U.S. manufacturing workforce. For a priori interests, the observed to expected episodes of care ratios were comparable for fluorochemical and film plant employees for liver tumors or diseases, bladder cancer, thyroid and lipid metabolism disorders, and reproductive, pregnancy, and perinatal disorders and higher for biliary tract disorders and cystitis recurrence. Non-a priori associations among the fluorochemical plant workers included benign colon polyps, malignant colorectal tumors, and malignant melanoma.				●						-		C	B
761	ヒト（肝毒性）	Olsen, G W; Burris, J M; Burlew, M M; Mandel, J H	Plasma cholecystokinin and hepatic enzymes, cholesterol and lipoproteins in ammonium perfluorooctanoate production workers	2018	Drug Chem Toxicol. 2000 Nov;23(4):603-20. doi: 10.1081/dct-100101973.	Ammonium perfluorooctanoate is a potent synthetic surfactant used in industrial applications. It rapidly dissociates in biologic media to perfluorooctanoate [CF3(CF2)6CO2-], which is the anion of perfluorooctanoic acid [PFOA, CF3(CF2)6COOH]. PFOA is a peroxisome proliferator known to increase the incidence of hepatic, pancreas and Leydig cell adenomas in rats. The pancreas acinar cell adenomas may be the consequence of a mild but sustained increase of cholecystokinin as a result of hepatic cholestasis. Although no significant clinical hepatic toxicity was observed, PFOA was reported to have modulated hepatic responses to obesity and alcohol consumption among production workers. To further assess these hypotheses, we examined medical surveillance data of male workers involved in ammonium perfluorooctanoate production in 1993 (n=111), 1995 (n=80) and 1997 (n=74). Serum PFOA was measured by high-performance liquid chromatography mass spectrometry methods. Plasma cholecystokinin was measured (only in 1997) by the use of direct radioimmunoassay. Serum biochemical tests included hepatic enzymes, cholesterol and lipoproteins. Serum PFOA levels, by year, were: 1993 (mean 5.0 ppm, SD 12.2, median 1.1 ppm, range 0.0-80.0 ppm); 1995 (mean 6.8 ppm, SD 16.0, median 1.2 ppm, range 0.0-114.1 ppm); and 1997 (mean 6.4 ppm, SD 14.3, median 1.3 ppm, range 0.1-81.3 ppm). Cholecystokinin values (mean 28.5 pg/ml, SD 17.1, median 22.7 pg/ml, range 8.8-86.7 pg/ml) approximated the assay's reference range (up to 80 pg/ml) for a 12 hour fast and were negatively, not positively, associated with employees' serum PFOA levels. Our findings continue to suggest there is no significant clinical hepatic toxicity associated with PFOA levels as measured in this workforce. Unlike a previously reported observation, PFOA did not appear to modulate hepatic responses to either obesity or alcohol consumption. Limitations of these findings include: 1) the cross-sectional design as only 17 subjects were common for the three surveillance years; 2) the voluntary participation that ranged between 50 and 70 percent; and 3) the few subjects with serum levels > or = 10 ppm.				●			●			-		C	B
762	ヒト（肝毒性）	Olsen, G W; Burris, J M; Mandel, J H; Zobel, L R	Serum perfluorooctane sulfonate and hepatic and lipid clinical chemistry tests in fluorochemical production employees	2018	J Occup Environ Med. 1999 Sep;41(9):799-806. doi: 10.1097/00043764-199909000-00012.	The 3M Company manufactures fluorochemicals, which have as a precursor perfluorooctane sulfonyl fluoride (C8F17SO2F). These compounds may be expected to transform metabolically, to an undetermined degree, to perfluorooctane sulfonate (PFOS, C8F17SO3-) as an end-stage metabolite. Subchronic studies in rats and primates indicate a potential for cumulative toxicity with PFOS with the primary effect related to metabolic wasting with hypolipidemia as a consistent finding. Biennial medical surveillance has been offered to the company's fluorochemical production workers located in Decatur, Alabama, and Antwerp, Belgium. In 1995, the mean serum PFOS level, as measured by high-performance liquid chromatography mass spectrometry, for 178 male employees was 2.19 parts per million (ppm; range, 0.00 to 12.83 ppm), and in 1997, for 149 male employees, it was 1.75 ppm (0.10 to 9.93 ppm). Our analyses suggest that among these production employees, there were no substantial changes in serum hepatic enzymes, cholesterol, or lipoproteins associated with PFOS levels less than 6 ppm. It was not possible to derive inferences from the few employees who had serum PFOS levels > or = 6 ppm. These results may be due to the lower levels of serum PFOS measured among these production employees, compared to those suspected to cause effects in laboratory animals.				●						-		C	B
763	ヒト（肝毒性）	Sakr, Carine J; Leonard, Robin C; Kreckmann, Kim H; Slade, Martin D; Cullen, Mark R	Longitudinal study of serum lipids and liver enzymes in workers with occupational exposure to ammonium perfluorooctanoate	2019	J Occup Environ Med. 2007 Aug;49(8):872-9. doi: 10.1097/JOM.0b013e318124a93f.	OBJECTIVE: To examine the relationship between serum perfluorooctanoate (PFOA), a biomarker of ammonium perfluorooctanoate exposure, and lipids and liver enzymes. METHODS: We conducted a longitudinal study on 454 workers and used mixed models to examine the relationship between serum PFOA and lipids and liver enzymes. RESULTS: One part per million (ppm) increase in serum PFOA was associated with a 1.06 mg/dL increase in total cholesterol, but was not associated with changes in triglycerides or other lipoproteins, after adjusting for potential confounders. Serum PFOA was also associated with total bilirubin (0.008 mg/dL decline/ppm) and serum aspartate aminotransferase (0.35 units increase/ppm) but not with the other liver enzymes. CONCLUSIONS: These medical surveillance data collected on workers for up to 25 years contributes useful information on the effects of ammonium perfluorooctanoate exposure on human liver and lipid chemistry.				●		●	●			-		C	B
764	ヒト（肝毒性）	Steenland, Kyle; Fletcher, Tony; Savitz, David A	Epidemiologic evidence on the health effects of perfluorooctanoic acid (PFOA)	2010	Environ Health Perspect. 2010 Aug;118(8):1100-8. doi: 10.1289/ehp.0901827. Epub 2010 Apr 27.	OBJECTIVE AND SOURCES: We reviewed the epidemiologic literature for PFOA. DATA SYNTHESIS: Perfluorooctanoic acid (PFOA) does not occur naturally but is present in the serum of most residents of industrialized countries (U.S. median, 4 ng/mL). Drinking water is the primary route of exposure in some populations, but exposure sources are not well understood. PFOA has been used to manufacture such products as Gore-Tex and Teflon. PFOA does not break down in the environment; the human half-life is estimated at about 3 years. PFOA is not metabolized in the body; it is not lipophilic. PFOA is not directly genotoxic; animal data indicate that it can cause several types of tumors and neonatal death and may have toxic effects on the immune, liver, and endocrine systems. Data on the human health effects of PFOA are sparse. There is relatively consistent evidence of modest positive associations with cholesterol and uric acid, although the magnitude of the cholesterol effect is inconsistent across different exposure levels. There is some but much less consistent evidence of a modest positive correlation with liver enzymes. Most findings come from cross-sectional studies, limiting conclusions. Two occupational cohort studies do not provide consistent evidence for chronic disease; both are limited by sample size and reliance on mortality data. Reproductive data have increased recently but are inconsistent, and any observed adverse effects are modest. CONCLUSIONS: Epidemiologic evidence remains limited, and to date data are insufficient to draw firm conclusions regarding the role of PFOA for any of the diseases of concern.				●		●				-		C	C
765	ヒト（肝毒性）	Yamaguchi, Miwa; Arisawa, Kokichi; Uemura, Hirokazu; Katsuura-Kamano, Sakurako; Takami, Hidenobu; Sawachika, Fusakazu; Nakamoto, Mariko; Juta, Tomoya; Toda, Eisaku; Mori, Kei; Hasegawa, Manabu; Tanto, Masaharu; Shima, Masayuki; Sumiyoshi, Yoshio; Morinaga, Kenji; Kodama, Kazunori; Suzuki, Takaichiro; Nagai, Masaki; Satoh, Hiroshi	Consumption of seafood, serum liver enzymes, and blood levels of PFOS and PFOA in the Japanese population	2013	J Occup Health. 2013;55(3):184-94. doi: 10.1539/joh.12-0264-oa. Epub 2013 Apr 9.	OBJECTIVE: Perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) have been shown to accumulate in the human body. The purpose of the present study was to examine the factors associated with the blood levels of PFOS and PFOA. METHODS: A cross-sectional study was performed on 307 men and 301 women (aged 16-76 years) living in 15 prefectures in Japan. Blood levels of PFOS and PFOA were measured by liquid chromatography-mass spectrometry. Hepatic enzymes (γ-GTP, GOT, and GPT) and ω-3 polyunsaturated fatty acids (DHA and EPA) levels in serum were also measured. Associations between the levels of PFOS and PFOA in blood and the intake frequency of 41 kinds of dishes, foods and beverages and the serum levels of liver enzymes and ω-3 polyunsaturated fatty acids were examined using rank correlations. RESULTS: Frequency of intake of boiled fish in broth, sliced raw fish and coastal fish showed significant positive correlations with PFOS concentrations in blood after adjustments for potential confounders. Serum levels of GOT, GPT, DHA and EPA showed significant positive correlations with PFOS and PFOA in blood. There was also a significant regional difference in the blood levels of PFOS and 2013PFOA, with medians being highest in the Tokai/Hokuriku/Kinki region. CONCLUSIONS: These findings suggest that the concentrations of PFOS in blood were mainly associated with fish consumption and that the levels of PFOS and PFOA were associated with the serum levels of liver enzymes in Japanese populations. Further investigations are required to clarify the reason for the regional differences in blood levels of PFOS and PFOA in Japan.				●						-		C	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報抽出対象	文献ランク①	文献ランク②
766	ヒト（肝毒性）	Zeng XW, Qian Z, Emo B.	Association between perfluoroalkyl chemicals and serum lipid levels in children	2015	Sci Total Environ. 2015 Apr 15;512-513:364-370. doi: 10.1016/j.scitotenv.2015.01.042. Epub 2015 Jan 30.	Perfluoroalkyl and polyfluoroalkyl substances (PFASs), as well as polymers of PFASs, have been widely used in commercial applications and have been detected in humans and the environment. Previous epidemiological studies have shown associations between particular PFAS chemicals and serum lipid concentrations in adults, particularly perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA). There exists, however, limited information concerning the effect of PFASs have on serum lipids among children. In the present cross sectional study, 225 Taiwanese children (12–15 years of age) were recruited to determine the relationship between serum level PFASs and lipid concentration. Results showed that eight out of ten particular PFASs were detected in the serum of N94% of the participants. Serum PFOS and perfluorotetradecanoic acid (PFTA) levels were at an order of magnitude higher than the other PFASs, with arithmetical means of 32.4 and 30.7 ng/ml in boys and 34.2 and 27.4 ng/ml in girls, respectively. However, the variation in serum PFTA concentration was quite large. Following covariate adjustment, linear regression models revealed that PFOS, PFOA, and perfluorononanoic acid (PFNA) were positively associated with total cholesterol (TC), low-density lipoprotein (LDL) and triglycerides (TG), particularly for PFOS and PFTA. Quartile analysis, with the lowest exposure quartile as a reference, yielded associations between serum PFTA and elevations in TC (p = 0.002) and LDL (p = 0.004). Though not statistically significant, high-density lipoprotein (HDL) appeared to decrease linearly across quartiles for PFOS and PFOA exposure. In conclusion, a significant association was observed between serum PFASs and lipid level in Taiwanese children. These findings for PFTA are novel, and emphasize the need to investigate the exposure route and toxicological evidence of PFASs beyond PFOS and PFOA.				●						アブスト入力もれ、要確認	1	D	D
767	ヒト（肝毒性）	Attanasio, Roberta	Association between perfluoroalkyl acids and liver function: Data on sex differences in adolescents	2019	Data Brief. 2019 Oct 5;27:104618. doi: 10.1016/j.dib.2019.104618. eCollection 2019 Dec.	The data herein presented show multivariate linear regressions performed to examine the association between individual serum perfluoroalkyl acids (PFAAs) [perfluorooctane sulfonic acid (PFOS); linear form of perfluorooctanoic acid (PFOA); perfluorohexane sulfonic acid (PFHxS); perfluorononanoic acid (PFNA)], and biomarkers of liver function (Sex Differences in the association between perfluoroalkyl compounds and liver function in US adolescents: analyses of NHANES 2013-2016). Data relate to male and female adolescents (ages 12-19 years) who participated to the 2013-2016 National Health and Nutrition Examination Survey. The outcome of interest was represented by changes in biomarkers of liver function, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT). Serum measurement values of ALT, AST and GGT were natural log-transformed. Data represent multivariate regression analyses with the single PFAA as β coefficients (and 95%CI), adjusted by age, race/ethnicity, body weight, education, income-to-poverty ratio, and exposure to smoking. Single PFAAs were used as continuous natural log-transformed predicted variables in males and females. Analyses were performed also with individuals PFAAs categorized via sex-specific weighted quartile, with cutoffs based on the weighted distribution of the single PFAA in the study population. Because the dependent variables (ALT, AST and GGT) were log-transformed, data were re-transformed by exponentiation of the β coefficients, and presented as percent differences estimated by comparing each of the upper three quartiles to the lowest quartile using the formula 100*(e(β) -1). Together, these data can serve as a basis to analyze associations between liver function and PFAA exposure taking into account sex differences in adolescent populations.		●								-		C	B
768	ヒト（代謝）	Alderete, T. L.; Jin, R.; Walker, D. I.; Valvi, D.; Chen, Z.; Jones, D. P.; Peng, C.; Gilliland, F. D.; Berhane, K.; Conti, D. V.; Goran, M. I.; Chatzi, L.	Perfluoroalkyl substances, metabolomic profiling, and alterations in glucose homeostasis among overweight and obese Hispanic children: A proof-of-concept analysis	2019	Environ Int. 2019 May;126:445-453. doi: 10.1016/j.envint.2019.02.047. Epub 2019 Mar 4.	OBJECTIVE: To examine the prospective associations between exposure to perfluoroalkyl substances (PFASs) and longitudinal measurements of glucose metabolism in high-risk overweight and obese Hispanic children.METHODS: Forty overweight and obese Hispanic children (8-14 years) from urban Los Angeles underwent clinical measures and 2-hour oral glucose tolerance tests (OGTT) at baseline and a follow-up visit (range: 1-3 years after enrollment). Baseline plasma perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), perfluorohexane sulfonic acid (PFHxS), and the plasma metabolome were measured by liquid-chromatography with high-resolution mass spectrometry. Multiple linear regression models were used to assess the association between baseline PFASs and changes in glucose homeostasis over follow-up. A metabolome-wide association study coupled with pathway enrichment analysis was performed to evaluate metabolic dysregulation associated with plasma PFASs concentrations. We performed a structural integrated analysis aiming to characterize the joint impact of all factors and to identify latent clusters of children with alterations in glucose homeostasis, based on their exposure and metabolomics profile.RESULTS: Each ln (ng/ml) increase in PFOA and PFHxS concentrations was associated with a 30.6 mg/dL (95% CI: 8.8-52.4) and 10.2 mg/dL (95% CI: 2.7-17.7) increase in 2-hour glucose levels, respectively. A ln (ng/ml) increase in PFHxS concentrations was also associated with 17.8 mg/dL increase in the glucose area under the curve (95% CI: 1.5-34.1). Pathway enrichment analysis showed significant alterations of lipids (e.g., glycosphingolipids, linoleic acid, and de novo lipogenesis), and amino acids (e.g., aspartate and asparagine, tyrosine, arginine and proline) in association to PFASs exposure. The integrated analysis identified a cluster of children with increased 2-h glucose levels over follow up, characterized by increased PFAS levels and altered metabolite patterns.CONCLUSIONS: This proof-of-concept analysis shows that higher PFAS exposure was associated with dysregulation of several lipid and amino acid pathways and longitudinal alterations in glucose homeostasis in Hispanic youth. Larger studies are needed to confirm these findings and fully elucidate the underlying biological mechanisms.	●	●								-	1	A	B
769	ヒト（代謝）	Buck, C. O.; Eliot, M. N.; Kelsey, K. T.; Calafat, A. M.; Chen, A.; Ehrlich, S.; Lanphear, B. P.; Braun, J. M.	Prenatal exposure to perfluoroalkyl substances and adipocytokines: the HOME Study	2018	Pediatr Res. 2018 Dec;84(6):854-860. doi: 10.1038/s41390-018-0170-1. Epub 2018 Sep 13.	OBJECTIVE: Gestational perfluoroalkyl substances exposure has been associated with decreased birthweight. We determined if gestational perfluoroalkyl substances exposure was associated with fetal metabolic markers using data from the HOME Study, a prospective birth cohort of pregnant women and their children in Cincinnati, Ohio.METHODS: Maternal serum concentrations of perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorononanoic acid, and perfluorohexane sulfonic acid were quantified. We measured neonatal adipocytokine (leptin and adiponectin) concentrations in umbilical cord serum, and estimated percent differences with a 2-fold increase in maternal perfluoroalkyl substances concentrations among 230 mother-infant pairs.RESULTS: Median maternal serum PFOA and PFOS concentrations were 5.6 ng/mL and 14 ng/mL, respectively. Leptin was positively correlated with infant birthweight ($p < 0.001$). There were no statistically significant associations between maternal perfluoroalkyl substances and neonatal adipocytokine concentrations; each 2-fold increase in PFOA was associated with a non-significant increase in leptin (5%; 0.95 CI: -10, 22) and adiponectin (7%; 0.95 CI: -4, 19).CONCLUSION: Despite known associations with reduced birthweight, gestational serum perfluoroalkyl substances concentrations were not associated with neonatal adipocytokine concentrations. Further exploration of pathways of perfluoroalkyl substances associated changes in birthweight may help identify biomarkers that could be used to identify at-risk populations and develop interventions.	●	●								-		B	B
770	ヒト（発がん性）	C8 Science Panel	C8 portable link reports	2012	C8 portable link reports. http://www.c8sciencepanel.org/prob_link.html	No abstract available	●	●							●	C8 science panel ウェブサイト公表資料。対象外とする		D	-
771	ヒト（代謝）	Canova, C.; Barbieri, G.; Zare Jeddi, M.; Gion, M.; Fabricio, A.; Daprà, F.; Russo, F.; Fletcher, T.; Pitter, G.	Associations between perfluoroalkyl substances and lipid profile in a highly exposed young adult population in the Veneto Region	2020	Environ Int. 2020 Dec;145:106117. doi: 10.1016/j.envint.2020.106117. Epub 2020 Sep 21.	Background: Residents of a large area of the Veneto Region (North-Eastern Italy) were exposed for decades to drinking water contaminated by perfluoroalkyl substances (PFAS). PFAS have been consistently associated with raised serum lipids, mainly in cross-sectional studies and in background exposure contexts, but the shape of the dose-response relationships has been poorly investigated. The objectives of our study were to evaluate the association between serum PFAS and serum lipids and their dose-response patterns in a large exposed population. Methods: A cross-sectional study was conducted in 16,224 individuals aged 20-39 years recruited in the regional health surveillance program. 15,720 subjects were analysed after excluding pregnant women (n = 327), participants reporting use of cholesterol lowering medications (n = 67) or with missing information on the selected covariates (n = 110). Twelve PFAS were measured by HPLC-MS in serum; three (PFOA, PFOS and PFHxS) were quantifiable in at least 50% of samples. Non-fasting serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and triglycerides were measured by enzymatic assays in automated analysers and low-density lipoprotein cholesterol (LDL-C), non-HDL cholesterol and total/HDL cholesterol ratio were calculated. The associations between natural log (ln) transformed PFAS and lipids were assessed through generalized additive models using linear regression and smoothing thin plate splines, adjusted for potential confounders. Results: There were strong positive associations between the ln-transformed PFOA, PFOS, and PFHxS and TC, HDL-C, and LDL-C, and between ln PFOA and PFHxS and triglycerides. Each ln-increase in PFOA was associated with an increase of 1.94 mg/dL (95% CI 1.48-2.41) in TC, with 4.99 mg/dL (CI 4.12-5.86) for PFOS and 2.02 mg/dL (CI 1.45-2.58) for PFHxS. Conclusions: Investigation of the shape of exposure-response associations using splines showed a positive association with the largest increases per unit of PFAS in cholesterol levels occurring at the lower range of PFAS concentrations for each compound.	●	●							●	-		D	D

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ラン①抽出	文献ラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
772	ヒト（代謝）	Cardenas, A.; Gold, D. R.; Hauser, R.; Kleinman, K. P.; Hivert, M. F.; Calafat, A. M.; Ye, X.; Webster, T. F.; Horton, E. S.; Oken, E.	Plasma concentrations of per- and polyfluoroalkyl substances at baseline and associations with glycemic indicators and diabetes incidence among high-risk adults in the Diabetes Prevention Program trial	2017	Environ Health Perspect. 2017 Oct 2;125(10):107001. doi: 10.1289/EHP1612.	BACKGROUND: Several per- and polyfluoroalkyl substances (PFAS) are ubiquitous anthropogenic pollutants almost universally detected in humans. Experimental evidence indicates that PFAS alter glucose metabolism and insulin secretion. However, epidemiological studies have yielded inconsistent results.OBJECTIVE: We sought to examine associations between plasma PFAS concentrations, glycemic indicators, and diabetes incidence among high-risk adults.METHODS: Within the Diabetes Prevention Program (DPP), a trial for the prevention of type 2 diabetes among high-risk individuals, we quantified baseline plasma concentrations of nine PFAS among 957 participants randomized to a lifestyle intervention or placebo. We evaluated adjusted associations for plasma PFAS concentrations with diabetes incidence and key glycemic indicators measured at baseline and annually over up to 4.6 y.RESULTS: Plasma PFAS concentrations were similar to those reported in the U.S. population in 1999-2000. At baseline, in cross-sectional analysis, a doubling in plasma perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) concentrations was associated with higher homeostatic model assessment of insulin resistance (HOMA-IR) [βPFOS=0.39; 0.95 confidence interval (CI): 0.13, 0.66; βPFOA=0.64; 0.95 CI: 0.34, 0.94], β-cell function (HOMA-β) (βPFOS=9.62; 0.95 CI: 1.55, 17.70; βPFOA=15.93; 0.95 CI: 6.78, 25.08), fasting proinsulin (βPFOS=1.37 pM; 0.95 CI: 0.50, 2.25; βPFOA=1.71 pM; 0.95 CI: 0.72, 2.71), and glycated hemoglobin (HbA1c) (βPFOS=0.03%; 0.95 CI: 0.002, 0.07; βPFOA=0.04%; 0.95 CI: 0.001, 0.07). There was no strong evidence of associations between plasma PFAS concentrations and diabetes incidence or prospective changes in glycemic indicators during the follow-up period.CONCLUSIONS: At baseline, several PFAS were cross-sectionally associated with small differences in markers of insulin secretion and β-cell function. However, there was limited evidence suggesting that PFAS concentrations are associated with diabetes incidence or changes in glycemic indicators during the follow-up period.	●	●	●	●						-		1	A	A
773	ヒト（代謝）	Cardenas, A.; Hivert, M. F.; Gold, D. R.; Hauser, R.; Kleinman, K. P.; Lin, P. D.; Fleisch, A. F.; Calafat, A. M.; Ye, X.; Webster, T. F.; Horton, E. S.; Oken, E.	Associations of perfluoroalkyl and polyfluoroalkyl substances with incident diabetes and microvascular disease	2019	Diabetes Care. 2019 Sep;42(9):1824-1832. doi: 10.2337/dc18-2254. Epub 2019 Jul 11.	OBJECTIVE: Perfluoroalkyl and polyfluoroalkyl substances (PFASs) are suspected endocrine disruptors widely detected across populations. We examine the extent to which PFASs are associated with diabetes incidence and microvascular disease. Secondarily, we tested whether a lifestyle intervention modifies associations and decreases concentrations.RESEARCH DESIGN AND METHODS: We analyzed data from a prospective cohort of 957 participants from the Diabetes Prevention Program (DPP) trial and Diabetes Prevention Program Outcomes Study (DPPOS). At baseline, participants were randomized to an intensive lifestyle intervention of diet, physical activity, and behavior modification or a placebo medication. We quantified plasma concentrations of six PFASs at baseline and 2 years after randomization. Participants were monitored for ~15 years, repeatedly tested for diabetes, and evaluated for microvascular disease at the end of the follow-up.RESULTS: A doubling in baseline branched perfluorooctanoic acid concentration was associated with a 0.14 increase in diabetes risk for the placebo (hazard ratio [HR] 1.14, 0.95 CI 1.04, 1.25) but not in the lifestyle intervention group (HR 1.01, 0.95 CI 0.92, 1.11, Pinteraction = 0.11). Mean change in plasma baseline branched perfluorooctanoic acid concentration was greater for the placebo (0.96 ng/mL; 0.95 CI 0.71, 1.22) compared with the lifestyle intervention group (0.31 ng/mL; 0.95 CI 0.14, 0.48) 2 years after randomization. Each doubling in N-ethyl-perfluorooctane sulfonamido acetic acid was associated with 0.17 greater odds of prevalent microvascular disease (OR 1.17, 0.95 CI 1.05, 1.31), and a similar association was observed for perfluorodimethylhexane sulfonic acid (OR 1.18, 0.95 CI 1.04, 1.35), regardless of treatment.CONCLUSIONS: Some plasma PFASs were associated with diabetes and microvascular disease. Our results suggest that exercise and diet may attenuate the diabetogenic association of PFASs.	●	●								-			A	C
774	ヒト（代謝）	Carmichael, S.; Abrams, B.; Selvin, S.	The pattern of maternal weight gain in women with good pregnancy outcomes	1997	Am J Public Health. 1997 Dec;87(12):1984-8. doi: 10.2105/ajph.87.12.1984.	OBJECTIVES: This study describes the pattern of maternal weight gain in women with good pregnancy outcomes and provides data to fill in the provisional weight-gain charts published by the Institute of Medicine (IOM) in 1990.METHODS: We selected 7002 women with good outcomes (defined by factors related to maternal and infant health) from the University of California, San Francisco, Perinatal Database. For each body mass index category, we compared percentiles of weight gain by trimester in women who achieved the IOM recommendations for total gain and those who did not.RESULTS: Trimester rates of gain varied by body mass index category and exceeded IOM guidelines in all groups. Forty percent of these women with good outcomes had total gains within the guidelines and provided data to complete the IOM weight-gain charts.CONCLUSIONS: Most women in this good-outcome sample would have been suspected of being at increased risk for poor outcome on the basis of their weight gain. This confirms the IOM recommendation that evaluation of the underlying causes of excessively high or low weight gain during pregnancy is necessary before appropriate interventions can be applied.	●	●								-			C	C
775	ヒト（代謝）	Chen, A.; Jandarov, R.; Zhou, L.; Calafat, A. M.; Zhang, G.; Urbina, E. M.; Sarac, J.; Augustin, D. H.; Caric, T.; Bockor, L.; Petranovic, M. Z.; Novokmet, N.; Missoni, S.; Rudan, P.; Deka, R.	Association of perfluoroalkyl substances exposure with cardiometabolic traits in an island population of the eastern Adriatic coast of Croatia	2019	Sci Total Environ. 2019 Sep 15;683:29-36. doi: 10.1016/j.scitotenv.2019.05.250. Epub 2019 May 20.	BACKGROUND: Exposure to perfluoroalkyl substances (PFAS), ubiquitous environmental contaminants, may be related to cardiometabolic diseases in adults. Studies in European populations to examine the association of PFAS exposure and comprehensive cardiometabolic traits and metabolic syndrome (MetS) are limited.METHODS: In this pilot cross-sectional study of a well-characterized adult population of the island of Hvar, situated off the eastern Adriatic coast of Croatia, we measured PFAS concentrations in plasma samples collected during 2007-2008 and examined their cross-sectional associations with cardiometabolic traits and MetS after adjustment of covariates (n = 122). PFAS investigated in this study included perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorohexane sulfonic acid (PFHxS), and perfluorononanoic acid (PFNA).RESULTS: The geometric mean (range) was 8.91 (2.36, 33.67) ng/mL for PFOS, 2.87 (1.03, 8.02) ng/mL for PFOA, 0.77 (0.25, 2.40) ng/mL for PFHxS, and 1.29 (0.48, 3.46) ng/mL for PFNA, with frequency of detection at 100%, 100%, 95.9%, and 100%, respectively. PFOS, PFOA, and PFNA concentrations were positively associated with the risk of MetS as defined by the Adult Treatment Panel III (ATP III) criteria, with estimated odds ratios and 0.95 confidence intervals at 1.89 (0.93, 3.86), 2.19 (0.88, 5.44), and 2.95 (1.12, 7.80), respectively, with only PFNA reaching	●	●								-		1	A	B
776	ヒト（代謝）	Chen, Q.; Zhang, X.; Zhao, Y.; Lu, W.; Wu, J.; Zhao, S.; Zhang, J.; Huang, L.	Prenatal exposure to perfluorobutanesulfonic acid and childhood adiposity: A prospective birth cohort study in Shanghai, China	2019	Chemosphere. 2019 Jul;226:17-23. doi: 10.1016/j.chemosphere.2019.03.095. Epub 2019 Mar 19.	BACKGROUND: Several per- and polyfluoroalkyl substances (PFAS) have been phased out due to their adverse effects, and replaced by the short-chain perfluorobutanesulfonic acid (PFBS). However, the long-term impacts of PFBS on human health are unknown.OBJECTIVE: We aimed to investigate the association between prenatal exposure to PFAS, especially PFBS and childhood adiposity at 5 years of age.METHODS: We conducted a prospective birth cohort study involving 1140 pregnant women from 2012 to 2017 in Shanghai. Fetal umbilical cord blood was collected at birth. A total of 404 children (196 girls) completed the adiposity measurements using a bioelectrical impedance analysis method and cord plasma PFAS measurements using LC-MS/MS. Multivariable linear models after adjustment for potential confounders were used to evaluate the associations between PFAS and childhood adiposity.RESULTS: The median concentration of PFAS in the cord plasma ranged from 0.05 (PFBS) to 6.74 ng/mL (PFOA). Results of multivariable linear regression found that in girls, PFBS had a significant positive association with waist circumference and waist to height ratio (P-values < 0.05). Girls in the highest tertile of PFBS concentrations had more fat mass, as well as higher body fat percentage, waist circumference, and waist to height ratio compared to those in the lowest tertile. However, girls in the second tertile of PFDoA had lower body fat percentage, waist circumference and fat mass.CONCLUSIONS: Adiposity at 5 years of age shows a positive association with prenatal exposure to PFBS in girls. These findings need to be further verified in larger prospective studies.	●	●								-			C	B
777	ヒト（代謝）	Christensen, K. Y.; Raymond, M.; Meiman, J.	Perfluoroalkyl substances and metabolic syndrome	2019	Int J Hyg Environ Health. 2019 Jan;222(1):147-153. doi: 10.1016/j.ijheh.2018.08.014. Epub 2018 Oct 2.	BACKGROUND: Perfluoroalkyl substances (PFAS) are a class of contaminants used in many industrial applications and consumer products. Certain PFAS are regulated or voluntarily limited due to concern about environmental persistence and adverse health effects.OBJECTIVES: In this analysis we examine PFAS levels and their association with metabolic syndrome and its components, using a representative sample of the U.S.POPULATION: METHODS: Data on PFAS levels and metabolic syndrome components were collected from the 2007-2008, 2009-2010, 2011-2012, and 2013-2014 cycles of the National Health and Nutrition Examination Survey. Twelve different PFAS were measured in serum samples from participants. Logistic regression models were used to identify associations between metabolic syndrome, its individual components, and serum PFAS concentrations.RESULTS: Over one-third -0.37 of participants met the definition for metabolic syndrome, with increased waist circumference and elevated glucose being the most commonly reported components. Seven PFAS were detected in at least 0.3 of participants and were examined in subsequent analyses (PFDA, PFOA, PFOS, PFHxS, MPAH, PFNA, PFUnDA). The PFAS with the highest concentrations was PFOS (median 8.4 ng/mL), followed by PFOA, PFHxS and PFNA. After adjusting for potential confounders, PFNA was associated with increased risk of metabolic syndrome and well as several individual components, while the highest levels of PFHxS were associated with elevated triglycerides. Other PFAS were associated with decreased risk of at least one outcome.CONCLUSIONS: Associations between PFAS and metabolic syndrome are inconsistent within and across studies. PFNA was consistently associated with increased risk for components of the syndrome, a finding that warrants further investigation.	●	●								-		1	B	A

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①抽出	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
778	ヒト（代謝）	Christensen, K. Y.; Raymond, M.; Thompson, B. A.; Anderson, H. A.	Perfluoroalkyl substances in older male anglers in Wisconsin	2016	Environ Int. 2016 May;91:312-8. doi: 10.1016/j.envint.2016.03.012. Epub 2016 Mar 19.	BACKGROUND: Perfluoroalkyl substances (PFAS) are an emerging class of contaminants. Certain PFAS are regulated or voluntarily limited due to concern about environmental persistence and adverse health effects, including thyroid disease and to dyslipidemia. The major source of PFAS exposure in the general population is seafood.OBJECTIVES: In this analysis we examine PFAS levels and their determinants, as well as associations between PFAS levels and self-reported health outcomes, in a group of older male anglers in Wisconsin with high fish consumption.METHODS: A biomonitoring study of male anglers aged 50 and older living in Wisconsin collected detailed information on fish consumption, demographics and self-reported health outcomes, along with hair and blood samples for biomarker analysis. Sixteen different PFAS were extracted from serum samples. Regression models were used to identify factors (demographic characteristics and fish consumption habits) associated with PFAS biomarker levels in blood, as well as associations between PFAS and self-reported health outcomes, adjusting for potential confounders.RESULTS: Seven PFAS were detected in at least 0.3 of participants and were used in subsequent analyses (PFDA, PFHpS, PFHxS, PFNA, PFOA, PFOS, PFuDA). The PFAS with the highest levels were PFOS, followed by PFOA, PFHxS and PFNA (medians of 19.0, 2.5, 1.8 and 1.4ng/mL). In general, increasing age was associated with higher PFAS levels, while increasing BMI were associated with lower PFAS levels. Greater alcohol consumption was associated with higher levels of PFHpS, PFHxS and PFOA. Associations with smoking and employment did not show a consistent pattern. Associations between fish consumption and PFAS were generally weak, with the exception of notably higher PFDA and PFHpS with both other locally-caught fish, and restaurant-purchased fish. Regarding associations with health outcomes, PFuDA, PFNA and PFDA were all associated with increased risk of pre-diabetes and/or diabetes. PFHpS was associated with a significantly increased risk of high cholesterol; PFDA and PFuDA also showed notable, though non-significant associations. All PFAS evaluated were associated with lower risk of hypertension although the only significant odds ratio was that for PFNA. There were no associations between any of the PFAS examined and either coronary heart disease, or the grouped outcome of any cardiovascular condition.CONCLUSIONS: PFAS are emerging contaminants with widespread exposure, persistence, and potential for adverse health effects. In this study population, demographic patterns may reflect differences in exposure sources, or possibly differences in adsorption and metabolism. PFAS were associated mainly with endocrine related outcomes, with a	●	●		●			●			-	1	B	A
779	ヒト（代謝）	Convertino, M.; Church, T. R.; Olsen, G. W.; Liu, Y.; Doyle, E.; Elcombe, C. R.; Barnett, A. L.; Samuel, L. M.; Macpherson, I. R.; Evans, T. R. J.	Stochastic pharmacokinetic-pharmacodynamic modeling for assessing the systemic health risk of perfluorooctanoate (pfoa)	2018	Toxicol Sci. 2018 May 1;163(1):293-306. doi: 10.1093/toxsci/kfy035.	A phase 1 dose-escalation trial assessed the chemotherapeutic potential of ammonium perfluorooctanoate (APFO). Forty-nine primarily solid-tumor cancer patients who failed standard therapy received weekly APFO doses (50-1200 mg) for 6 weeks. Clinical chemistries and plasma PFOA (anionic APFO) were measured predose and weekly thereafter. Several clinical measures including total cholesterol, high-density lipoproteins (HDLs), thyroid stimulating hormone (TSH), and free thyroxine (fT4), relative to PFOA concentrations were examined by: Standard statistical analyses using generalized estimating equations (GEE) and a probabilistic analysis using probability distribution functions (pdf) at various PFOA concentrations; and a 2-compartment pharmacokinetic/pharmacodynamic (PK/PD) model to directly estimate mean changes. Based on the GEE, the average rates of change in total cholesterol and fT4 associated with increasing PFOA were approximately -1.2×10-3 mmol/l/μM and 2.8×10-3 pmol/l/μM, respectively. The PK/PD model predicted more closely the trends observed in the data as well as the pdfs of biomarkers. A decline in total cholesterol was observed, with a clear transition in shape and range of the pdfs, manifested by the maximum value of the Kullback-Leibler (KL) divergence, that occurred at plasma PFOA between 420 and 565 μM (175 000-230 000 ng/ml). High-density lipoprotein was unchanged. An increase in fT4 was observed at a higher PFOA transition point, albeit TSH was unchanged. Our findings are consistent with some animal models and may motivate re-examination of the epidemiologic studies to PFOA at levels several orders of magnitude lower than this study. These observational studies have reported contrary associations, but currently understood biology does not support the existence of such conflicting effects.	●	●	●	●				●	●	-	1	B	A
780	ヒト（代謝）	Conway, B.; Innes, K. E.; Long, D.	Perfluoroalkyl substances and beta cell deficient diabetes	2016	J Diabetes Complications. 2016 Aug;30(6):993-8. doi: 10.1016/j.jdiacomp.2016.05.001. Epub 2016 May 4.	AIMS: Perfluoroalkyl substances (PFAS) are synthetic hydrocarbons shown to preserve pancreatic islet cell viability and reduce islet cell hypoxia and apoptosis. We investigated the relationship of serum PFAS with diabetes, and whether this varied by diabetes type.METHODS: 6,460 individuals with and 60439 without diabetes from the C8 Health Project, were categorized into three groups: type 1 (n=820), type 2 (n=4,291), or uncategorized diabetes (n=1,349, missing data on diabetes type or diabetes based on blood sugar at study entry). Four PFAS were investigated: perfluorohexane sulfonate (PFHxS), perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), and perfluorononaoic acid (PFNA).RESULTS: PFAS levels were significantly lower in those with diabetes, and lowest in those with type 1 diabetes. In age and sex adjusted analyses, ORs (CI) for type 1, type 2, and uncategorized diabetes compared to no diabetes were 0.59 (0.54-0.64), 0.74 (0.71-0.77), 0.84 (0.78-0.90), respectively for PFHxS; 0.69 (0.65-0.74), 0.87 (0.89-0.91), 0.92 (0.88-0.97), respectively for PFOA; 0.65 (0.61-0.70), 0.86 (0.82-0.90), 0.93 (0.86-1.03), respectively for PFOS; and 0.65 (0.57-0.74), 0.94 (0.88-1.00), 0.95 (0.85-1.06), respectively for PFNA. Further adjustment for eGFR and other covariates did not eliminate these inverse associations.CONCLUSIONS: PFAS levels were negatively associated with diabetes. This inverse relationship was strongest for type 1 diabetes, suggesting the relationship with serum PFAS may vary with the severity of islet cell deficiency.	●	●		●						-		B	B
781	ヒト（代謝）	Dewey, K. G.; Heinig, M. J.; Nommsen, L. A.	Maternal weight-loss patterns during prolonged lactation	1993	Am J Clin Nutr. 1993 Aug;58(2):162-6. doi: 10.1093/ajcn/58.2.162.	Weight and triceps-skinfold thickness were measured until 24 mo postpartum in matched cohorts of women who breast-fed for > or = 12 mo (BF; n = 46) or < or = 3 mo (FF; n = 39). In the BF group, breast-feeding frequency and breast-milk energy output were determined every 3 mo until 18 mo. Weight loss from 1 to 12 mo postpartum was significantly greater in BF than in FF women (4.4 vs 2.4 kg, P < 0.05), due primarily to differences in weight loss from 3 to 6 mo. BF mothers had a net loss in triceps-skinfold thickness whereas FF mothers gained fat at this site (-0.4 vs 2.4 mm, P < 0.05). Breast-feeding frequency and total time breast-feeding were related to weight loss in the BF group from 6 to 12 mo. Maternal weight did not differ significantly between 12 and 24 mo in either group. We conclude that lactation enhances weight loss postpartum if breast-feeding continues for at least 6 mo.	●	●								-		C	C
782	ヒト（代謝）	Domazet, S. L.; Grøntved, A.; Timmermann, A. G.; Nielsen, F.; Jensen, T. K.	Longitudinal associations of exposure to perfluoroalkylated substances in childhood and adolescence and indicators of adiposity and glucose metabolism 6 and 12 years later: The European Youth Heart Study	2016	Diabetes Care. 2016 Oct;39(10):1745-51. doi: 10.2337/dc16-0269. Epub 2016 Aug 3.	OBJECTIVE: To investigate the long-term association of exposure to perfluoroalkylated substances, including perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA), during childhood (9 years) and adolescence (15 years) on indicators of adiposity and glucose metabolism in adolescence (15 years) and young adulthood (21 years). Secondarily, we aim to clarify the degree of tracking of exposure from childhood into young adulthood.RESEARCH DESIGN AND METHODS: Data derived from a large multicenter prospective cohort study, in which the same participants have been observed from childhood (N = 590), during adolescence (N = 444), and into young adulthood (N = 369). Stored plasma samples were analyzed for PFOS and PFOA. Indicators of adiposity comprising body height, body weight, sum of four skinfolds, and waist circumference, as well as indicators of glucose metabolism, comprising fasting blood glucose, triglyceride, and insulin levels, β-cell function, and insulin resistance, have been collected at all study waves. Multiple linear regression was applied in order to model earlier exposure on later outcome while controlling for baseline outcome levels, sex, age, and socioeconomic factors.RESULTS: Childhood exposure to PFOS was associated with indicators of adiposity at 15 years of age that are displayed in elevated BMI, skinfold thickness, and waist circumference, as well as increased skinfold thickness and waist circumference at 21 years of age. PFOA exposure in childhood was associated with decreased β-cell function at 15 years of age. We did not observe associations between exposure during adolescence and indicators of adiposity and glucose metabolism in young adulthood.CONCLUSIONS: This study found evidence for childhood exposure to PFOS and PFOA predicting adiposity at 15 and 21 years of age and impaired β-cell function at 15 years of age, respectively.	●	●		●						-	1	A	B
783	ヒト（代謝）	Domazet, S. L.; Jensen, T. K.; Wedderkopp, N.; Nielsen, F.; Andersen, L. B.; Grøntved, A.	Exposure to perfluoroalkylated substances (PFAS) in relation to fitness, physical activity, and adipokine levels in childhood: The European youth heart study	2020	Environ Res. 2020 Dec;191:110110. doi: 10.1016/j.envres.2020.110110. Epub 2020 Aug 29.	Background: perfluoroalkylated substances (PFAS) are highly persistent chemicals that are able to alter the human metabolism - potentially via disruption of cell signaling pathways mediated by adipokines. Both adiponectin and leptin are influenced by and exert influence on energy storage and energy expenditure, wherefore associations between PFAS and adipokines may be mediated by fitness and fat mass. Objectives: the aim of this cross-sectional study was to investigate the association between childhood exposure to PFAS and adipokines (adiponectin and leptin), while considering associations between PFAS and children's level of fitness, physical activity and fat mass to elucidate potential mediation by fitness, physical activity and fat mass. Methods: 9-year old children from Danish public schools were recruited in the European Youth Heart Study in 1997. For this study only children with valid measures on PFAS (PFOS, PFOA, PFNA, PFDA and PFHxS), adipokines (adiponectin and leptin), fitness, fat mass and co-variates (parity and maternal income) were included (N = 242). Multiple linear regression models with and without conditioning and causal mediation analysis were applied. Results: this study found inverse associations between PFOA, PFDA and PFHxS and leptin. PFOA was positively associated with adiponectin, whereas PFHxS was inversely associated with adiponectin in boys. Latter association seemed to be mediated by fat mass. Associations with leptin showed indirect effects of fitness and fat mass but were unable to demonstrate significant mediation. Neither PFOS nor PFNA were associated with the outcome. Discussion: these results may indicate a favorable leptin profile with increasing PFAS, although the results could be driven by residual negative confounding from socio-economic factors and mediation by fitness and fat mass.	●	●								-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
784	ヒト（代謝）	Donat-Vargas, C.; Bergdahl, I. A.; Tornevi, A.; Wennberg, M.; Sommar, J.; Kiviranta, H.; Koponen, J.; Rolandsson, O.; Åkesson, A.	Perfluoroalkyl substances and risk of type II diabetes: A prospective nested case-control study	2019	Environ Int. 2019 Feb;123:390-398. doi: 10.1016/j.envint.2018.12.026. Epub 2018 Dec 19.	BACKGROUND: Perfluoroalkyl substances (PFAS) have drawn much attention due to bioaccumulation potential and their current omnipresence in human blood. We assessed whether plasma PFAS, suspected to induce endocrine-disrupting effects, were prospectively associated with clinical type 2 diabetes (T2D) risk.METHODS: We established a nested case-control study within the Swedish prospective population-based Västerbotten Intervention Programme cohort. Several PFAS were measured in plasma from a subset of 124 case-control pairs at baseline (during 1990-2003) and at 10-year follow-up. T2D cases were matched (1:1) according to gender, age and sample date with participants without T2D (controls). Conditional logistic regressions were used to prospectively assess risk of T2D by baseline PFAS plasma concentrations. Associations between long-term PFAS plasma levels (mean of baseline and follow-up) and insulin resistance (HOMA2-IR) and beta-cell function (HOMA2-B%) at follow-up were prospectively explored among 178 and 181 controls, respectively, by multivariable linear regressions.RESULTS: After adjusting for gender, age, sample year, diet and body mass index, the odds ratio of T2D for the sum of PFAS (Σ z-score PFAS) was 0.52 (95% confidence interval, CI: 0.20, 1.36), comparing third with first tertile; and 0.92 (95% CI: 0.84, 1.00) per one standard deviation increment of sum of log-transformed PFAS. Among the controls, the adjusted β of HOMA2-IR and HOMA-B% for the sum of PFAS were -0.26 (95% CI: -0.52, -0.01) and -9.61 (95% CI: -22.60, 3.39) respectively comparing third with first tertile.CONCLUSIONS: This prospective nested case-control study yielded overall inverse associations between individual PFAS and risk of T2D, although mostly non-significant. Among participants without T2D, long-term PFAS exposure was prospectively associated with lower insulin resistance.	●	●							-		B	B
785	ヒト（代謝）	Donat-Vargas, C.; Bergdahl, I. A.; Tornevi, A.; Wennberg, M.; Sommar, J.; Koponen, J.; Kiviranta, H.; Åkesson, A.	Associations between repeated measure of plasma perfluoroalkyl substances and cardiometabolic risk factors	2019	Environ Int. 2019 Mar;124:58-65. doi: 10.1016/j.envint.2019.01.007. Epub 2019 Jan 10.	Background: Perfluoroalkyl substances (PFAS) are persistent synthetic chemicals that may affect components of metabolic risk through the peroxisome proliferator-activated receptor but epidemiological data remain scarce and inconsistent.	●	●	●						-		D	C
786	ヒト（代謝）	Dong, Z.; Wang, H.; Yu, Y. Y.; Li, Y. B.; Naidu, R.; Liu, Y.	Using 2003-2014 U	2019	Ecotoxicol Environ Saf. 2019 May 30;173:461-468. doi: 10.1016/j.ecoenv.2019.02.061. Epub 2019 Feb 21.	Exposure to per- and polyfluoroalkyl substances (PFASs) is a major concern due to their widespread occurrence and adverse health outcomes. The possible binding of PFASs to peroxisome proliferator-activated receptors (PPARs) and nuclear receptors raises concerns that PFASs may impact cholesterol levels in human. In this study, the U.S. National Health and Nutrition Examination Survey (NHANES) data were employed to address the temporal trend for PFAS concentrations in biomonitoring and associations between cholesterol levels and PFAS exposure. Compared to the PFAS levels in 2003-2004, the median perfluorooctanoic acid (PFOA), perfluorooctanesulfonic acid (PFOS), perfluorohexane sulfonic acid (PFHxS) and perfluorononanoic acid (PFNA) levels in human serum in 2013-2014 decreased from 3.7 to 1.8 ng/mL, 19.2-4.7 ng/mL, 1.7 ng/mL to 1.3 ng/mL and 0.8 ng/mL to 0.6 ng/mL, respectively. Also, an estimate of 1.5 ± 0.7 mg/dL (95% confidence interval: 0.2 - 2.8) and 0.4 ± 0.2 mg/dL (95% confidence interval: 0.1 - 0.6) total cholesterol increases for unit PFOA and PFOS increase (ng/mL), respectively. By using hybrid approach, RfDs were estimated to be 2.0 ng PFOS/kg per day and 0.8 ng PFOA/kg per day. However, it should be cautious when using proposed RfDs based on data obtained from cross-sectional datasets, especially evidence based on data originating from experimental or animal studies is still controversial.	●	●	●						-		A	C
787	ヒト（代謝）	Duan, Y.; Sun, H.; Yao, Y.; Meng, Y.; Li, Y.	Distribution of novel and legacy per-/polyfluoroalkyl substances in serum and its associations with two glycemic biomarkers among Chinese adult men and women with normal blood glucose levels	2020	Environ Int. 2020 Jan;134:105295. doi: 10.1016/j.envint.2019.105295. Epub 2019 Nov 11.	In recent years, the occurrence of novel per-/polyfluoroalkyl substances (PFASs) such as polyfluoroalkyl ether sulfonates (PFAESs) in human samples have aroused attention due to the change in PFASs production profile, however, the data are still lacking. Furthermore, epidemiological studies have examined the associations of PFAS exposure with glucose homeostasis, but with inconsistent results. Therefore, in this study, fasting serum samples from 252 participants with an age range from 19 to 87 years old were collected in Tianjin, China. A total of 21 target PFASs were determined to analyze the levels and distribution of novel and legacy PFASs in serum and to further evaluate the cross-sectional associations of serum PFAS concentrations with two glycemic biomarkers (i.e., fasting glucose and glycated hemoglobin (HbA1c)). 0.251388888888889 chlorinated PFAES (6:2 Cl-PFAES) and trifluoroacetic acid (TFA) were widely detected novel PFASs (greater than90%) with relatively high median concentrations (8.64 ng/mL and 8.46 ng/mL, respectively), which were second only to the two dominant legacy PFASs, i.e., perfluorooctanoic acid (PFOA, 14.83 ng/mL) and perfluorooctane sulfonic acid (14.24 ng/mL). The percentage contributions to the total known PFASs were separately 0.176 and 0.172 for 0.251388888888889 Cl-PFAES and TFA. The levels of 0.251388888888889 Cl-PFAES were significantly correlated with age and BMI, and the concentrations of TFA were also significantly correlated with age. Furthermore, 0.01 increase in serum PFOA and perfluorononanoic acid (PFNA) was separately significantly associated with 0.00018 [95% confidence interval (CI): 0.004%, 0.033%] and 0.00022 (95% CI: 0.007%, 0.037%) increment in fasting glucose levels. Similarly, 0.01 increase in serum perfluorohexanoic acid, PFNA, and perfluorohexane sulfonic acid was significantly associated with 0.0003 (95% CI: 0.010%, 0.051%), 0.00018 (95% CI: 0.003%, 0.033%), 0.00007 (95% CI: 0.003%, 0.011%) increment in HbA1c levels, respectively. These findings suggested that 0.251388888888889 Cl-PFAES and TFA showed greater contributions to PFASs in serum and supported an association of exposure to PFASs with fasting glucose and HbA1c.	●	●							-		B	B
788	ヒト（代謝）	Fan, Y.; Lu, C.; Li, X.; Xu, Q.; Zhang, Y.; Yang, X.; Han, X.; Du, G.; Xia, Y.; Wang, X.	Serum albumin mediates the effect of multiple per- and polyfluoroalkyl substances on serum lipid levels	2020	Environ Pollut. 2020 Nov;266(Pt 2):115138. doi: 10.1016/j.envpol.2020.115138. Epub 2020 Jul 19.	Perfluoroalkyl and polyfluoroalkyl substances (PFASs) are synthetically manufactured chemicals recognized to be toxic, bioaccumulative, and persistent. Previous studies on PFAS exposure and serum lipid levels have mainly focused on individual PFASs; however, the influence of multiple-PFAS exposure on the serum lipid profile remains unclear. This study was performed to evaluate the combined effects of multiple PFASs on serum lipid levels. Based on the National Health and Nutrition Examination Survey (NHANES) data (2011-2014), we first established a linear regression model to estimate the association between single-PFAS exposure and the serum lipid profile. Then, a weighted quantile sum (WQS) regression model and a Bayesian kernel machine regression (BKMR) model were used to evaluate the effects of multiple-PFAS exposure on the serum lipid profile. A mediating effect model was used to assess how albumin mediates these effects. We found that PFASs were significantly associated with the levels of serum lipids, including high-density lipoprotein (HDL), low-density lipoprotein (LDL) and total cholesterol (TC). The WQS index was significantly correlated with the levels of HDL (beta: 2.03, 0.95 CI: 0.74-3.32, P-value = 0.002), LDL (beta: 4.16, 0.95 CI: 1.07-7.24, P-value = 0.008) and TC (beta: 6.54, 0.95 CI: 3.00-10.1, P-value < 0.001). In the BKMR analysis, our results demonstrated that the effect of PFASs on serum lipids increased significantly when the concentrations of the PFASs were at their 60th percentiles or above compared to those at their 50th percentile. Mediation analysis showed that albumin mediated the effects of selected PFASs on the levels of serum lipids except for triglycerides (TG). PFAS exposure was correlated with the levels of serum lipids, and this correlation was mediated by albumin. Our results suggest that a comprehensive evaluation of multi-PFAS exposure could better characterize real-life exposure compared with single-PFAS exposure.	●	●							-	1	B	A
789	ヒト（代謝）	Fassler, C. S.; Pinney, S. E.; Xie, C.; Biro, F. M.; Pinney, S. M.	Complex relationships between perfluorooctanoate, body mass index, insulin resistance and serum lipids in young girls	2019	Environ Res. 2019 Sep;176:108558. doi: 10.1016/j.envres.2019.108558. Epub 2019 Jun 26.	BACKGROUND: Perfluorooctanoate (PFOA) has been used extensively in the manufacture of both commercial and household products. PFOA serum concentrations have been associated with adverse health effects, including lower body mass in children and infants.OBJECTIVE: To determine if there is an association between serum PFOA concentration and body mass, serum insulin and lipid profile in exposed young girls.METHODS: We conducted a cross-sectional study of PFAS environmental biomarkers and insulin resistance in 6 to 8 year-old girls from Greater Cincinnati (n=353). In 2004-2006, blood samples were obtained to measure polyfluoroalkyl substances (PFAS), fasting insulin, glucose and lipids. Clinical exams included anthropometric measurements and pubertal maturation staging. Linear regression and mediation analyses, specifically structural equation modeling (SEM), were used to determine the strength and direction of the relationships between PFAS, pubertal maturation status, body mass index (BMI), cholesterol and insulin resistance.RESULTS: The median PFOA (7.7ng/ml) was twice the National Health and Nutrition Examination Survey (2005-2006). Only PFOA, a PFAS sub-species, showed statistically significant relationships with the outcomes. In regression models, PFOA was associated with decreased BMI and waist-to-height ratio (p=0.0008; p=0.0343), HDL-cholesterol (p=0.0046) and had a borderline inverse association with the HOMA Index of insulin resistance (p=0.0864). In SEM, PFOA retained an inverse relationship with BMI (p<0.0001) but the relationships with HOMA and HDL-cholesterol were no longer statistically significant. Pubertal initiation (Tanner breast or pubic stage 2 or greater) and BMI were associated with increased HOMA Index (p<0.0001).CONCLUSIONS: These findings suggest PFOA exposure in young girls affects both BMI and ultimately insulin resistance. In mediation analysis with puberty in the model, the direct effects of PFOA on insulin resistance and were reduced.	●	●							-		B	B
790	ヒト（代謝）	Fleisch, A. F.; Rifas-Shiman, S. L.; Mora, A. M.; Calafat, A. M.; Ye, X.; Luttmann-Gibson, H.; Gillman, M. W.; Oken, E.; Sagiv, S. K.	Early-life exposure to perfluoroalkyl substances and childhood metabolic function	2017	Environ Health Perspect. 2017 Mar;125(3):481-487. doi: 10.1289/EHP303. Epub 2016 Sep 2.	BACKGROUND: Perfluoroalkyl substances (PFASs) are synthetic chemicals that may persist in the environment and in humans. There is a possible association between early-life PFAS exposure and metabolic dysfunction in later life, but data are limited.METHODS: We studied 665 mother-child pairs in Project Viva, a Boston, Massachusetts-area cohort recruited 1999-2002. We quantified concentrations of PFASs [perfluorooctanoate (PFOA), perfluorooctane sulfonate (PFOS), perfluorononanoate (PFNA), perfluorohexane sulfonate (PFHxS), and perfluorodecanoate (PFDeA)] in maternal plasma collected at the first prenatal visit (median, 9.6 weeks gestation) and in child plasma from the mid-childhood research visit (median, 7.7 years). We assessed leptin, adiponectin, and homeostatic model assessment of insulin resistance (HOMA-IR) in mid-childhood. We fit covariate-adjusted linear regression models and conducted stratified analyses by child sex.RESULTS: Children with higher PFAS concentrations had lower HOMA-IR [e.g., -0.101 (95% CI: -17.3, -2.3) per interquartile range increment in PFOA]. This inverse association between child PFAS and HOMA-IR was more pronounced in females [e.g., PFOA: -0.156 (95% CI: -25.4, -4.6) vs. -0.061 (95% CI: -16.2, 5.2) for males]. Child PFAS plasma concentrations were not associated with leptin or adiponectin. Prenatal PFAS plasma concentrations were not associated with leptin, adiponectin, or HOMA-IR in offspring.CONCLUSIONS: We found no evidence for an adverse effect of early-life PFAS exposure on metabolic function in mid-childhood. In fact, children with higher PFAS concentrations had lower insulin resistance. Citation: Fleisch AF, Rifas-Shiman SL, Mora AM, Calafat AM, Ye X, Luttmann-Gibson H, Gillman MW, Oken E, Sagiv SK. 2017 Early-life exposure to perfluoroalkyl substances and childhood metabolic function.	●	●	●	●					-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ラン①抽出	文献ラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
791	ヒト（代謝）	Fragki, S.; Dirven, H.; Fletcher, T.; Grasl-Kraupp, B.; Bjerve Gützkow, K.; Hoogenboom, R.; Kersten, S.; Lindeman, B.; Louisse, J.; Peijnenburg, A.; Piersma, A. H.; Princen, H. M. G.; Uhl, M.; Westerhout, J.; Zeilmaker, M. J.; Luijten, M.	Systemic PFOS and PFOA exposure and disturbed lipid homeostasis in humans: what do we know and what not? Crit Rev Toxicol141-164	2021	Crit Rev Toxicol. 2021 Feb;51(2):141-164. doi: 10.1080/10408444.2021.1888073. Epub 2021 Apr 15.	Associations between per- and polyfluoroalkyl substances (PFASs) and increased blood lipids have been repeatedly observed in humans, but a causal relation has been debated. Rodent studies show reverse effects, i.e. decreased blood cholesterol and triglycerides, occurring however at PFAS serum levels at least 100-fold higher than those in humans. This paper aims to present the main issues regarding the modulation of lipid homeostasis by the two most common PFASs, PFOS and PFOA, with emphasis on the underlying mechanisms relevant for humans. Overall, the apparent contrast between human and animal data may be an artifact of dose, with different molecular pathways coming into play upon exposure to PFASs at very low versus high levels. Altogether, the interpretation of existing rodent data on PFOS/PFOA-induced lipid perturbations with respect to the human situation is complex. From a mechanistic perspective, research on human liver cells shows that PFOS/PFOA activate the PPARα pathway, whereas studies on the involvement of other nuclear receptors, like PXR, are less conclusive. Other data indicate that suppression of the nuclear receptor HNF4α signaling pathway, as well as perturbations of bile acid metabolism and transport might be important cellular events that require further investigation. Future studies with human-relevant test systems would help to obtain more insight into the mechanistic pathways pertinent for humans. These studies shall be designed with a careful consideration of appropriate dosing and toxicokinetics, so as to enable biologically plausible quantitative extrapolations. Such research will increase the understanding of possible perturbed lipid homeostasis related to PFOS/ PFOA exposure and the potential implications for human health.	●	●								-		B	B
792	ヒト（代謝）	Graber, J. M.; Alexander, C.; Laumbach, R. J.; Black, K.; Strickland, P. O.; Georgopoulos, P. G.; Marshall, E. G.; Shendell, D. G.; Alderson, D.; Mi, Z.; Mascari, M.; Weisel, C. P.	Per and polyfluoroalkyl substances (PFAS) blood levels after contamination of a community water supply and comparison with 2013-2014 NHANES	2019	J Expo Sci Environ Epidemiol. 2019 Mar;29(2):172-182. doi: 10.1038/s41370-018-0096-z. Epub 2018 Nov 27.	INTRODUCTION: Per and polyfluoroalkyl substances (PFAS), including perfluorononanoic acid (PFNA) and perfluorooctanoic acid (PFOA), were detected in the community water supply of Paulsboro New Jersey in 2009.METHODS: A cross-sectional study enrolled 192 claimants from a class-action lawsuit, not affiliated with this study, who had been awarded a blood test for 13 PFAS. Study participants provided their blood test results and completed a survey about demographics; 105 participants also completed a health survey. Geometric means, 25th, 50th, 75th, and 95th percentiles of exposure of PFNA blood serum concentrations were compared to that of the 2013-2014 NHANES, adjusted for reporting level. Associations between PFNA, PFOA, PFOS, and PFHxS and self-reported health outcomes were assessed using logistic regression.RESULTS: PFNA serum levels were 2.85 higher in Paulsboro compared with U.S. residents. PFNA serum levels were higher among older compared with younger, and male compared to female, Paulsboro residents. After adjustment for potential confounding, there was a significant association between increased serum PFNA levels and self-reported high cholesterol (OR: 1.15, 0.95 CI: 1.02, 1.29).DISCUSSION/CONCLUSION: Further investigation into possible health effects of PFAS exposure in Paulsboro and other community settings is warranted. Since exposure has ceased, toxicokinetics of PFAS elimination should be explored.	●	●	●						●	-		B	B
793	ヒト（代謝）	He, X.; Liu, Y.; Xu, B.; Gu, L.; Tang, W.	PFOA is associated with diabetes and metabolic alteration in US men: National Health and Nutrition Examination Survey 2003-2012	2018	Sci Total Environ. 2018 Jun 1;625:566-574. doi: 10.1016/j.scitotenv.2017.12.186. Epub 2017 Dec 30.	Exposure to perfluoroalkyl substances (PFAS) is associated with a range of adverse health effects. However, it remains unclear whether PFAS at environmentally relevant exposure levels are related to diabetes and metabolite concentrations in adults. Using cross-sectional data from 7904 adults (age≥20years) in the 2003-2012 National Health and Nutrition Examination Survey (NHANES), we examined the association of PFAS with the prevalence of diabetes and metabolite concentrations. A multivariate logistic regression was applied to investigate the associations of diabetes prevalence with serum perfluorooctanoate (PFOA), perfluorooctane sulfonate (PFOS), perfluorohexane sulfonate (PFHxS) and perfluorononanoate (PFNA) levels. A multivariate generalised linear regression was further performed to investigate the associations between PFAS exposure and some metabolites. We identified a strong positive association between serum PFOA and diabetes prevalence in men with an adjusted model (OR: 2.66, 0.95 CI: 1.63-4.35; P for trend=0.001). No significant association between serum PFOA and diabetes prevalence was observed in women (OR: 1.47, 0.95 CI: 0.88-2.46; P for trend=0.737). Furthermore, diabetes was not related to PFOS, PFHxS and PFNA, regardless of gender. In the gender-stratified generalised linear models, men and women with the highest PFOA levels demonstrated a 0.0143 (95% CI: 0.62%-2.34%) and a 0.0107 (95% CI: 0.27%-1.97%) greater increase in serum total cholesterol (P for trend=0.006 and 0.001) compared to those with the lowest PFOA levels. There were no significant associations between serum PFOA and other metabolites. These results provide epidemiological evidence that environment-related levels of serum PFOA may be positively associated with the prevalence of diabetes in men and with total cholesterol in adults. Further clinical and animal studies are urgently needed to elucidate putative causal relationships and shed light on the potential mode of action involved.	●	●		●						-	1	A	A
794	ヒト（代謝）	Hutcheson, R.; Innes, K.; Conway, B.	Perfluoroalkyl substances and likelihood of stroke in persons with and without diabetes	2020	Diab Vasc Dis Res. 2020 Jan-Feb;17(1):1479164119892223. doi: 10.1177/1479164119892223. Epub 2019 Dec 16.	OBJECTIVE: The main objective of this study is to evaluate the relationship of perfluoroalkyl substances with stroke and any modifying influence of diabetes.METHODS: Data on 3921 adults aged ⩾20 years with and 44285 without diabetes were drawn from the C8 Health Project. Four perfluoroalkyl substances were investigated: perfluorohexane sulphate, C8 - perfluorooctanoic acid, perfluoroctane sulfonate and perfluorononaoic acid.RESULTS: There were 238 cases of stroke among those with and 643 among those without diabetes. In analyses controlled for age, sex, race, diabetes duration, body mass index, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, C-reactive protein, kidney function and a history of smoking, a history of stroke was significantly inversely associated with serum perfluorohexane sulphate (odds ratio = 0.75, 0.64-0.88) and perfluoroctane sulfonate (odds ratio = 0.81, 0.70-0.90), but not perfluorooctanoic acid (odds ratio = 1.04, 0.94-1.15) or perfluorononaoic acid (odds ratio = 0.89, 0.70-1.14) among those with diabetes. Perfluoroalkyl substances demonstrated no association with stroke among those without diabetes (p interaction = 0.006 and 0.01 for perfluorohexane sulphate and perfluorooctanoic acid, respectively).CONCLUSION: In this large cross-sectional study, serum levels of perfluorohexane sulphate and perfluoroctane sulfonate were inversely associated with stroke among those with diabetes. Although mechanisms and implications for this diabetes-specific inverse relationship need to be further explored, our data suggest that perfluoroalkyl substances do not increase risk of stroke among persons with or without diabetes.	●	●								-		B	B
795	ヒト（代謝）	Jaacks, L. M.; Boyd Barr, D.; Sundaram, R.; Grewal, J.; Zhang, C.; Buck Louis, G. M.	Pre-Pregnancy Maternal Exposure to Persistent Organic Pollutants and Gestational Weight Gain: A Prospective Cohort Study	2016	Int J Environ Res Public Health. 2016 Sep 12;13(9):905. doi: 10.3390/ijerph13090905.	Persistent organic pollutants (POPs) have been implicated in the development of obesity in non-pregnant adults. However, few studies have explored the association of POPs with gestational weight gain (GWG), an important predictor of future risk of obesity in both the mother and offspring. We estimated the association of maternal pre-pregnancy levels of 63 POPs with GWG. Data are from women (18-40 years; n = 218) participating in a prospective cohort study. POPs were assessed using established protocols in pre-pregnancy, non-fasting blood samples. GWG was assessed using three techniques: -1 total GWG (difference between measured pre-pregnancy weight and final self-reported pre-delivery weight); -2 category based on pre-pregnancy body mass index (BMI)-specific Institute of Medicine (IOM) recommendations; and -3 area under the GWG curve (AUC). In an exploratory analysis, effects were estimated separately for women with BMI < 25 kg/m² versus BMI ≥ 25 kg/m². Multivariable polytomous logistic regression and linear regression were used to estimate the association between each chemical or congener and the three GWG outcomes. p,p'-dichlorodiphenyl trichloroethane (p,p'-DDT) was significantly inversely associated with AUC after adjustment for lipids and pre-pregnancy BMI: beta {95% confidence interval (CI)}, -378.03 (-724.02, -32.05). Perfluorooctane sulfonate (PFOS) was significantly positively associated with AUC after adjustment for lipids among women with a BMI < 25 kg/m² {beta (95% CI), 280.29 (13.71, 546.86)}, but not among women with a BMI ≥ 25 kg/m² {beta (95% CI), 56.99 (-328.36, 442.34)}. In summary, pre-pregnancy levels of select POPs, namely, p,p'-DDT and PFOS, were moderately associated with GWG. The association between POPs and weight gain during pregnancy may be more complex than previously thought, and adiposity prior to pregnancy may be an important effect modifier.	●	●								-		B	C
796	ヒト（代謝）	Jain, R. B.	Concentration of selected liver enzymes across the stages of glomerular function: The associations with PFOA and PFOS	2019	Heliyon. 2019 Jul 29;5(7):e02168. doi: 10.1016/j.heliyon.2019.e02168. eCollection 2019 Jul.	Kidney function/dysfunction may affect liver function/dysfunction and vice versa. Liver function is indicated by the observed concentrations of several liver enzymes. Kidney function is indicated by the glomerular filtration rate. Consequently, it is logical to study associations between liver enzymes and glomerular filtration rate indicted by the stages of glomerular function (GF). Thus, this study was undertaken to evaluate the associations between selected liver enzymes and the stages of GF for US adults aged >= 20 years. Data (N = 9523) for US adults for the years 2003-2014 from National Health and Nutrition Examination Survey were analyzed to estimate variabilities in concentrations associated with liver enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphate (APH), and γ-glutamyl transferase (GGT) across the stages of GF and to assess variabilities in associations that perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS) may have with these enzymes across the stages of GF. Those with eGFR >90 mL/min/1.73 m2 were defined as being in GF-1, those with eGFR between 60 and 89 mL/min/1.73 m2 were defined as being in GF-2, those with eGFR between 45 and 59 mL/min/1.73 m2 were defined as being in GF-3A, those with eGFR between 15 and 44 mL/min/1.73 m2 were defined as being GF-3B/4. Regression models stratified by GF stages with ALT, AST, APH, and GGT as dependent variables were fitted to evaluate the associations of interest. Adjusted levels of ALT decreased with deteriorating kidney function from 25.3 IU/L at GF-1 to 20.9 IU/L at GF-3B/4 for obese adults and from 21.4 IU/L at GF-1 to 16.4 IU/L at GF-3B/4 for nonobese adults. Adjusted levels of AST followed inverted U-shaped distributions with increases from GF-1 to GF-2 followed by decreases from GF-2 to GF-3B/4. Adjusted levels of APH followed inverted U-shaped distributions with increases from GF-1 to GF-3A followed by decreases from GF-3A to GF-3B/4. Adjusted levels of GGT followed inverted U-shaped distribution among obese participants with point of inflection located at GF-3A. For the total population, obese had higher adjusted levels than nonobese at GF-1, GF-2, and GF-3A for ALT, APH, and GGT. Male-female differences in adjusted levels of ALT and GGT continued narrowing as kidney function deteriorated from GF-1 to GF-3B/4. The differences in ALT widened among nonobese smokers and nonsmokers as kidney function deteriorated. The concentrations of liver enzymes across GF stages varied by gender, race/ethnicity, smoking status, and obesity and more often than not, were	●	●	●							-		B	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報対象抽出	文献ランク①	文献ランク②
797	ヒト（代謝）	Jain, R. B.	Impact of the co-occurrence of obesity with diabetes, anemia, hypertension, and albuminuria on concentrations of selected perfluoroalkyl acids	2020	Environ Pollut. 2020 Nov;266(Pt 2):115207. doi: 10.1016/j.envpol.2020.115207. Epub 2020 Jul 17.	Data (N = 10644) for US adults aged ≥20 years for 2003-2016 from National Health and Nutrition Examination Survey were analyzed to evaluate the impact of co-occurrence of obesity with diabetes, anemia, albuminuria, and hypertension on concentrations of five perfluoroalkyl acids (PFAA), namely, perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorodecanoic acid (PFDA), perfluorohexane sulfonic acid (PFHxS), and perfluorononanoic acid (PFNA). For the total population, males, and females, co-occurrence of obesity with hypertension, albuminuria, anemia, and diabetes was found to be associated with lower adjusted geometric means (AGM) than nonobese for every PFAA. For example for females, for PFOS, AGMs for obese with no diseases, hypertension, albuminuria, anemia, and diabetes were 8.2, 10.8, 5.8, 4.6, and 7.7 ng/mL respectively. In comparison, for PFOS, for nonobese females, AGMs for those with no diseases, hypertension, albuminuria, anemia, and diabetes were found to be 8.9, 13.4, 7.7, 6.0, and 10.2 ng/mL respectively. This implies obesity is associated with higher excretion rates. Females, in general, had lower AGMs than males for both obese and nonobese for every PFAA for every disease group. For example, percent ratios of obese females to males AGMs for PFOA were 66.7%, 87.1%, 88.2%, 70.6%, and 0.9 for those with no diseases, hypertension, albuminuria, anemia, and diabetes respectively. The ratios of obese to nonobese AGMs for females were lower than males for every PFAA for those with no diseases and hypertension only. For example, for PFOA for those with no diseases, obese to nonobese AGM ratios were 0.87 for females and 1 for males. Thus, additional excretion of certain PFAAs due to obesity is higher in females than males for those with no diseases and hypertension only.	●	●								-		B	C
798	ヒト（代謝）	Jain, R. B.	Variabilities in concentrations of selected perfluoroalkyl acids among normotensives and hypertensives across various stages of glomerular function	2020	Arch Environ Occup Health. 2021;76(1):12-22. doi: 10.1080/19338244.2020.1732856. Epub 2020 Feb 26.	Data (N = 10643) from National Health and Nutrition Examination Survey for US adults aged > = 20 years for 2003-2016 were analyzed to evaluate how concentrations of selected perfluoroalkyl acids (PFAA) vary among normotensives and hypertensives across various stages of glomerular function (GF) namely from stage 1 to stage 3B/4. Regression models stratified by GF stages and hypertension status were fitted for each of the five PFAAs, namely, PFOA, PFOS, PFDA, PFHxS, and PFNA. For the total population, hypertensives had higher adjusted levels than normotensives for GF-1, GF-2, and GF-3A with highest differences being at GF-3A for every PFAA. At GF-3B/4, hypertensives had lower adjusted geometric means (AGM) than normotensives. While AGMs for PFAA for hypertensives followed inverted U-shaped distributions with points of inflections at GF-3A, for normotensives the points of inflections were at GF-2 or GF-3A.	●	●								-		B	C
799	ヒト（代謝）	Jain, R. B.; Ducatman, A.	Associations between lipid/lipoprotein levels and perfluoroalkyl substances among US children aged 6-11 years	2018	Environ Pollut. 2018 Dec;243(Pt A):1-8. doi: 10.1016/j.envpol.2018.08.060. Epub 2018 Aug 21.	Observed levels of lipid/lipoproteins are known to be associated with exposure to perfluoroalkyl substances (PFAS). In order to evaluate and update these associations among US children aged 44723 years, data (N = 458) from National Health and Nutrition Examination Survey for 2013-2014 were used. The associations between the observed levels of total cholesterol, high density lipoprotein (HDL) cholesterol, and non-HDL cholesterol and selected PFAS were studied. PFAS data were available for perfluorononanoic acid (PFNA), perfluorohexane sulfonate (PFHxS), linear isomer of perfluorooctanoic acid (PFOA), linear isomer of perfluorooctane sulfonate (PFOS), monomethyl branch isomer of PFOS, and sum of PFAS. Regression models were fitted to evaluate these associations. A statistically significant (p = 0.03) positive association between the levels of linear isomer of PFOS and total cholesterol was observed. A 0.1 increase in the levels of linear isomer of PFOS measured in ng/L was found to be accompanied by a 0.03-0.42% increase in the levels of total cholesterol measured in mg/dL. For PFNA, girls in the first quartile of PFNA were found to have lower adjusted levels for total cholesterol than the girls in the fourth quartile of PFNA (152.6 vs. 164.7 mg/dL, p < 0.01). Also, non-Hispanic blacks in the first quartile of PFNA were found to have lower adjusted levels for total cholesterol than the non-Hispanic blacks in the fourth quartile of PFNA (143.4 vs. 160.5 mg/dL, p = 0.04). A negative association between branch isomer of PFOS and non-HDL cholesterol was also observed (β = -0.0066, p = 0.04). The adjusted levels of non-HDL cholesterol were higher in the second quartile of ∑PFAS than in the fourth quartile of ∑PFAS (103.0 vs. 97.5 mg/dL, p < 0.01). Linear PFOS and possibly PFNA are associated with total cholesterol in the most recent NHANES childhood sample. Concentrations of PFAS and associations with cholesterol have both decreased compared to previous literature.	●	●								-	1	A	A
800	ヒト（代謝）	Jain, R. B.; Ducatman, A.	Selective associations of recent low concentrations of perfluoroalkyl substances with liver function biomarkers: nhanes 2011 to 2014 data on us adults aged ≥20 years	2019	J Occup Environ Med. 2019 Apr;61(4):293-302. doi: 10.1097/JOM.0000000000001532.	OBJECTIVE: Perfluoroalkyl substances (PFAS) and liver function biomarkers were reexamined for relatively lower serum concentrations of PFAS observed in recent years.METHODS: National Health and Nutrition Examination Survey 2011 to 2014 data were analyzed for obese and nonobese participants for serum perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), perfluorodecanoic acid (PFDA), perfluorohexane sulfonate (PFHxS), perfluorononanoic acid (PFNA) as well as four liver function biomarkers in risk-adjusted analysis.RESULTS: Among obese participants only, alanine aminotransferase (ALT) was positively associated with PFOA (β = 0.07065, P < 0.01), PFHxS (β = 0.051349, P < 0.01), and with PFNA (β = 0.072742, P < 0.01). PFOA (β = 0.07422, P = 0.03) and PFNA (β = 0.077995, P < 0.01) were associated with gamma glutamyl transferase (GGT) in obese participants.CONCLUSIONS: Recent lower levels of PFOA, PFHxS, and PFNA are associated with higher serum liver functions but only among obese participants. The findings are consistent with PFAS animal toxicology concerning steatosis.	●	●								-		B	B
801	ヒト（代謝）	Jeddy, Z.; Tobias, J. H.; Taylor, E. V.; Northstone, K.; Flanders, W. D.; Hartman, T. J.	Prenatal concentrations of perfluoroalkyl substances and bone health in British girls at age 17	2018	Archives of Osteoporosis. 2018 Aug 3;13(1):84. doi: 10.1007/s11657-018-0498-5.	Prenatal exposures to perfluoroalkyl substances (PFAS) have been associated with developmental outcomes in offspring. We found that prenatal concentrations of some PFAS may be associated with reduced bone mass and size in 17-year-old British girls, although it is not clear whether these associations are driven by body size.PURPOSE: PFAS are used to make protective coatings on common household products. Prenatal exposures have been associated with developmental outcomes in offspring. Using data from the Avon Longitudinal Study of Parents and Children (ALSPAC), we investigated the association between prenatal concentrations of PFAS and bone health in girls at 17 years of age and whether body composition can explain any associations.METHODS: We measured concentrations of perfluorooctane sulfonate (PFOS), perfluorooctanoate (PFOA), perfluorohexane sulfonate (PFHxS), and perfluorononanoic acid (PFNA) in maternal serum samples collected during pregnancy. We obtained bone health outcomes in the girls, such as bone mineral density, bone mineral content, bone area, and area-adjusted bone mineral content from whole-body dual-energy X-ray absorptiometry (DXA) scans. We used multivariable linear regression to explore associations between each PFAS and each bone health outcome with adjustment for important confounders such as girls' age at clinic visit, maternal education, and gestational age at sample collection. We also controlled for girls' height and lean mass to explore the role body composition had on observed associations.RESULTS: Prenatal PFOS, PFOA, PFHxS, and PFNA concentrations were associated with inverse effects on bone size and mass after adjusting for important confounders. Conversely, PFNA was positively associated with area-adjusted bone mineral content. However, most significant associations attenuated after additional controlling for height and lean mass.CONCLUSIONS: Prenatal concentrations of some PFAS may be associated with reduced bone mass and size in adolescent girls, although it is not clear whether these associations are driven by body size.	●	●								-		B	B
802	ヒト（代謝）	Jensen, R. C.; Glintborg, D.; Timmermann, C. A. G.; Nielsen, F.; Kyhl, H. B.; Andersen, H. R.; Grandjean, P.; Jensen, T. K.; Andersen, M.	Perfluoroalkyl substances and glycemic status in pregnant Danish women: The Odense Child Cohort	2018	Environ Int. 2018 Jul;116:101-107. doi: 10.1016/j.envint.2018.04.010. Epub 2018 Apr 13.	BACKGROUND: Perfluoroalkyl substances (PFASs) are persistent chemicals with suspected endocrine disrupting abilities applied in consumer products. PFASs have potentially modulating effects on glucose homeostasis. Insulin resistance prevails during third trimester of pregnancy, and this challenge of glucose homeostasis may reveal putative effects of PFAS concentrations on glycemic status.OBJECTIVE: To investigate associations between five serum PFASs and glucose-related outcomes in pregnant Danish women based on their risk of gestational diabetes mellitus (GDM).METHODS: In the prospective Odense Child Cohort serum concentrations of five PFASs - perfluorohexane sulfonic acid (PFHxS), perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA) and perfluorodecanoic acid (PFDA) - were measured at median gestational week (GW) 11 in pregnant women. An oral glucose tolerance test (OGTT) was performed at GW 28 The statistical analysis was conducted among 158 women with high GDM risk and 160 women with low GDM risk matched by gestational age. Multiple linear regression models were performed to estimate associations between PFAS concentrations and glucose, insulin, C-peptide, homeostatic model of assessment of insulin resistance (HOMA-IR) and beta cell function (HOMA-%β), and insulin sensitivity (Matsuda index) during the 2-h OGTT.RESULTS: In women with high risk for GDM, a two-fold increase in PFHxS concentration was significantly associated with increased fasting glucose, fasting insulin and HOMA-IR after adjusting for age, parity, educational level and pre-pregnancy BMI. Adjusting for the same confounders, a doubling in PFNA concentration was associated with higher fasting insulin and HOMA-%β. In women with low GDM risk, no associations were found between PFAS concentrations and glucose-related outcomes.CONCLUSION: PFHxS and PFNA concentrations were associated with impaired glycemic status in metabolically vulnerable pregnant women and might further enhance the risk of developing GDM.	●	●		●						-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
803	ヒト（代謝）	Khalil, N.; Ebert, J. R.; Honda, M.; Lee, M.; Nahhas, R. W.; Koskela, A.; Hangartner, T.; Kannan, K.	Perfluoroalkyl substances, bone density, and cardio-metabolic risk factors in obese 8-12 year old children: A pilot study	2018	Environ Res. 2018 Jan;160:314-321. doi: 10.1016/j.envres.2017.10.014. Epub 2017 Oct 15.	BACKGROUND AND OBJECTIVE: Perfluoroalkyl substances (PFASs), including perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorohexane sulfonic acid (PFHxS), and perfluorononanoic acid (PFNA), have been associated with adverse bone, and metabolic changes in adults. However association of PFASs with bone health in children is understudied. Considering their role as endocrine disruptors, we examined relationships of four PFASs with bone health in children.METHODS: In a cross sectional pilot study, 48 obese children aged 44785 years were enrolled from Dayton's Children Hospital, Ohio. Anthropometric, clinical and biochemical assessments of serum were completed. Serum PFASs were measured by UPLC-ESI-MS/MS. In a subset of 23 children, bone health parameters were measured using calcaneal quantitative ultrasound (QUS).RESULTS: While PFASs exposure was associated with a consistent negative relationship with bone health parameters, among four PFASs tested, only PFNA showed a significant negative relationship with bone parameter (β [95% CI], = - 72.7 [- 126.0, - 19.6], p = .010). PFNA was also associated with raised systolic blood pressure (p = .008), low density lipoprotein cholesterol (LDL-C; p < .001), and total cholesterol (TC; p = .014). In addition, both PFOA and PFOS predicted elevation in LDL-C, and PFOA predicted increased TC, as well. In this analysis, PFASs were not strongly related to thyroid hormones, 25-hydroxy vitamin D, liver enzymes, or glucose homeostasis.CONCLUSION: PFASs exposure in obese children may play a role in adverse skeletal and cardiovascular risk profiles.	●	●		●						-		B	B
804	ヒト（代謝）	Kim, Jin Hee; Park, Hye Yin; Jeon, Jung Dae; Kho, Younglim; Kim, Seung-Kyu; Park, Min-Seon; Hong, Yun-Chul	The modifying effect of vitamin C on the association between perfluorinated compounds and insulin resistance in the Korean elderly: a double-blind, randomized, placebo-controlled crossover trial	2016	Eur J Nutr. 2016 Apr;55(3):1011-20. doi: 10.1007/s00394-015-0915-0. Epub 2015 May 5.	PURPOSE: There is limited evidence whether environmental exposure to perfluorinated compounds (PFCs) affects insulin resistance (IR) and whether vitamin C intake protects against the adverse effect of PFCs. This study was carried out to investigate the effect of PFCs on IR through oxidative stress, and the effects of a 4-week consumption of vitamin C supplement compared placebo on development of IR by PFCs. METHODS: For a double-blind, community-based, randomized, placebo-controlled crossover intervention of vitamin C, we assigned 141 elderly subjects to both vitamin C and placebo treatments for 4 weeks. We measured serum levels of PFCs to estimate PFC exposures and urinary levels of malondialdehyde (MDA) and 8-hydroxy-2'-deoxyguanosine (8-OHdG) for oxidative stress. We also measured levels of fasting glucose and insulin and derived the homeostatic model assessment (HOMA) index to assess IR. RESULTS: Perfluorooctane sulfonate (PFOS) and perfluorododecanoic acid (PFDoDA) levels were found to be positively associated with HOMA index at the baseline and after placebo treatment. Risks of IR for the top decile of PFOS and PFDoDA exposures were significantly elevated compared with those with lower PFOS and PFDoDA exposures (both, P < 0.0001). However, the effects of PFOS and PFDoDA on HOMA disappeared after vitamin C supplementation (both, P > 0.30). Furthermore, PFOS and PFDoDA levels were also significantly associated with MDA and 8-OHdG levels, and MDA levels were positively associated with HOMA index. CONCLUSION: PFOS and PFDoDA exposures were positively associated with IR and oxidative stress, and vitamin C supplementation protected against the adverse effects of PFOS and PFDoDA on IR.	●	●								-		B	B
805	ヒト（代謝）	Lauritzen, H. B.; Larose, T. L.; Øien, T.; Sandanger, T. M.; Odland, J. Ø.; van de Bor, M.; Jacobsen, G. W.	Prenatal exposure to persistent organic pollutants and child overweight/obesity at 5-year follow-up: a prospective cohort study	2018	Environ Health. 2018 Jan 18;17(1):9. doi: 10.1186/s12940-017-0338-x.	BACKGROUND: Prenatal exposure to persistent organic pollutants (POPs), may influence offspring weight gain. More prospective epidemiological studies are needed to compliment the growing body of evidence from animal studies.METHODS: Serum from 412 pregnant Norwegian and Swedish women participating in a Scandinavian prospective cohort study were collected in 1986-88, and analyses of two perfluoroalkyl substances (PFASs) and five organochlorines (OCs) were conducted. We used linear and logistic regression models with 0.95 confidence intervals (CIs) to evaluate the associations between maternal serum POP concentrations at 17-20 weeks of gestation and child overweight/obesity (body mass index (BMI) ≥ 85th percentile) at 5-year follow-up. Results were further stratified by country after testing for effect modification. We also assessed potential non-monotonic dose-response (NMDR) relationships.RESULTS: In adjusted linear models, we observed increased BMI-for-age-and-sex z-score (β = 0.18, 0.95 CI: 0.01-0.35), and increased triceps skinfold z-score (β = 0.15, 0.95 CI: 0.02-0.27) in children at 5-year follow-up per ln-unit increase in maternal serum perfluorooctane sulfonate (PFOS) concentrations. We observed increased odds for child overweight/obesity (BMI ≥ 85th percentile) for each ln-unit increase in maternal serum PFOS levels (adjusted OR: 2.04, 0.95 CI: 1.11-3.74), with stronger odds among Norwegian children (OR: 2.96, 0.95 CI: 1.42-6.15). We found similar associations between maternal serum perfluorooctanoate (PFOA) concentrations and child overweight/obesity. We found indications of NMDR relationships between PFOS and polychlorinated biphenyl (PCB) 153 and child overweight/obesity among Swedish children.CONCLUSION: We found positive associations between maternal serum PFAS concentrations and child overweight/obesity at 5-year follow-up, particularly among Norwegian participants. We observed some evidence for NMDR relationships among Swedish participants.	●	●								-		B	B
806	ヒト（代謝）	Lin, C. Y.; Chen, P. C.; Lin, Y. C.; Lin, L. Y.	Association among serum perfluoroalkyl chemicals, glucose homeostasis, and metabolic syndrome in adolescents and adults	2009	Diabetes Care. 2009 Apr;32(4):702-7. doi: 10.2337/dc08-1816. Epub 2008 Dec 29.	OBJECTIVE: Perfluoroalkyl chemicals (PFCs) have been used worldwide in a variety of consumer products. The effect of PFCs on glucose homeostasis is not known.RESEARCH DESIGN AND METHODS: We examined 474 adolescents and 969 adults with reliable serum measures of metabolic syndrome profile from the National Health and Nutrition Examination Survey 1999-2000 and 2003-2004.RESULTS: In adolescents, increased serum perfluorononanoic acid (PFNA) concentrations were associated with hyperglycemia (odds ratio [OR] 3.16 [95% CI 1.39-7.16], P < 0.05). Increased serum PFNA concentrations also have favorable associations with serum HDL cholesterol (0.67 [0.45-0.99], P < 0.05). Overall, increased serum PFNA concentrations were inversely correlated with the prevalence of the metabolic syndrome (0.37 [0.21-0.64], P < 0.005). In adults, increased serum perfluorooctanoic acid concentrations were significantly associated with increased beta-cell function (beta coefficient 0.07 +/- 0.03, P < 0.05). Increased serum perfluorooctane sulfate (PFOS) concentrations were associated with increased blood insulin (0.14 +/- 0.05, P < 0.01), homeostasis model assessment of insulin resistance (0.14 +/- 0.05, P < 0.01), and beta-cell function (0.15 +/- 0.05, P < 0.01). Serum PFOS concentrations were also unfavorably correlated with serum HDL cholesterol (OR 1.61 [95% CI 1.15-2.26], P < 0.05).CONCLUSIONS: Serum PFCs were associated with glucose homeostasis and indicators of metabolic syndrome. Further clinical and animal studies are warranted to clarify putative causal relationships.	●	●	●	●			●			-		B	B
807	ヒト（代謝）	Lin, C. Y.; Lee, H. L.; Hwang, Y. T.; Su, T. C.	The association between total serum isomers of per- and polyfluoroalkyl substances, lipid profiles, and the DNA oxidative/nitrative stress biomarkers in middle-aged Taiwanese adults	2020	Environ Res. 2020 Mar;182:109064. doi: 10.1016/j.envres.2019.109064. Epub 2019 Dec 19.	Per- and polyfluoroalkyl substances (PFAS) have been widely used in consumer products. In vitro and animal studies have demonstrated that exposure to perfluorooctanoic acid (PFOA) and/or perfluorooctane sulfonate (PFOS) increases oxidative/nitrative stress. Recent studies have also found that isomers of PFOA/PFOS may have unique biological effects on clinical parameters. However, the correlation between PFOA/PFOS isomers and markers of oxidative/nitrative stress has never been investigated in the general population. In the current study, 597 adult subjects (ages between 22 and 63 years old) were enrolled from a control group of a case-control study entitled "Work-related risk factors and coronary heart disease". We investigated the correlation between the serum isomers of PFOA/PFOS, lipid profiles, and the urine compounds 8-hydroxy-2-deoxyguanosine (8-OHdG) and 8-nitroguanine (8-NO2Gua) in these participants. There were 519 men and 78 women with a mean age of 45.8 years. Linear PFOA levels were positively correlated with serum low density lipoprotein cholesterol (LDL-C), small dense LDL, and triglyceride, and linear PFOS levels were positively correlated with LDL-C and HDL-C in multiple linear regression analyses. After controlling for potential confounders, the mean levels of 8-OHdG and 8-NO2Gua significantly increased across the quartiles of linear PFOS in multiple linear regression analyses. When both the 8-OHdG and 8-NO2Gua levels were above the 50th percentile, the odds ratio (OR) of higher levels of LDL-C (>75th percentile) with one unit increase in ln linear PFOS level was the highest (OR 3.15 (95% CI = 1.45-6.64), P = 0.003) in logistic regression models. In conclusion, serum linear PFOA/PFOS were correlated with lipid profiles, and linear PFOS was associated with urine oxidative/nitrative stress biomarkers. The positive correlation between linear PFOS and LDL-C was more marked when concentrations of urine oxidative/nitrative stress biomarkers were elevated. Further studies are needed to elucidate the causal relationships among PFAS isomers, lipid profiles, and oxidative/nitrative stress.	●	●								-	1	B	A
808	ヒト（代謝）	Lind, L.; Zethelius, B.; Salihovic, S.; van Bavel, B.; Lind, P. M.	Circulating levels of perfluoroalkyl substances and prevalent diabetes in the elderly	2014	Diabetologia. 2014 Mar;57(3):473-9. doi: 10.1007/s00125-013-3126-3. Epub 2013 Dec 14.	AIMS/HYPOTHESIS: Several environmental contaminants, such as polychlorinated biphenyls, dioxins, bisphenol A and phthalates, have been linked to diabetes. We therefore investigated whether other kinds of contaminants, perfluoroalkyl substances (PFAS), also called perfluorinated compounds (PFCs), are also associated with diabetes.METHODS: The Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study investigated 1016 men and women aged 70 years. Seven PFAS were detected in almost all participant sera by ultra-high performance liquid chromatograph/tandem mass spectrometry. Diabetes was defined as use of hypoglycaemic agents or fasting glucose >7.0 mmol/l.RESULTS: 114 people had diabetes. In the linear analysis, no significant relationships were seen between the seven PFAS and prevalent diabetes. However, inclusion of the quadratic terms of the PFAS revealed a significant non-linear relationship between perfluorononanoic acid (PFNA) and diabetes, even after adjusting for multiple confounders (OR 1.96, 0.95 CI 1.19, 3.22, p = 0.008 for the linear term and OR 1.25, 0.95 CI 1.08, 1.44, p = 0.002 for the quadratic term). Perfluorooctanoic acid (PFOA) also showed such a relationship (p = 0.01). PFOA was related to the proinsulin/insulin ratio (a marker of insulin secretion), but none of the PFAS was related to the HOMA-IR (a marker of insulin resistance) following adjustment for multiple confounders. CONCLUSIONS/INTERPRETATION: PFNA was related to prevalent diabetes in a non-monotonic fashion in this cross-sectional study, supporting the view that this perfluoroalkyl substance might influence glucose metabolism in humans at the level of exposure seen in the general elderly population.	●	●	●	●						-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ラン①	文献ラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
809	ヒト（代謝）	Liu, G.; Zhang, B.; Hu, Y.; Rood, J.; Liang, L.; Qi, L.; Bray, G. A.; Dejonge, L.; Coull, B.; Grandjean, P.; Furtado, J. D.; Sun, Q.	Associations of Perfluoroalkyl substances with blood lipids and Apolipoproteins in lipoprotein subspecies: the POUNDS-lost study	2020	Environ Health. 2020 Jan 13;19(1):5. doi: 10.1186/s12940-020-0561-8.	BACKGROUND: The associations of perfluoroalkyl substance (PFAS) exposure with blood lipids and lipoproteins are inconsistent, and existing studies did not account for metabolic heterogeneity of lipoprotein subspecies. This study aimed to examine the associations between plasma PFAS concentrations and lipoprotein and apolipoprotein subspecies.METHODS: The study included 326 men and women from the 2-year Prevention of Obesity Using Novel Dietary Strategies (POUNDS) Lost randomized trial. Five PFASs, including perfluorooctanesulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorohexanesulfonic acid (PFHxS), perfluorononanoic acid (PFNA), and perfluorodecanoic acid (PFDA), were measured in plasma at baseline. For lipoprotein and apolipoprotein subspecies, total plasma was fractionated first by apolipoprotein (apo) C-III content and then by density. Each subfraction was then measured for apoB, apoC-III, and apoE concentrations, as well as triglyceride and cholesterol contents, both at baseline and at 2 years.RESULTS: For lipids and apolipoproteins in total plasma at baseline, elevated plasma PFAS concentrations were significantly associated with higher apoB and apoC-III concentrations, but not with total cholesterol or triglycerides. After multivariate adjustment of lifestyle factors, lipid-lowering medication use, and dietary intervention groups, PFAS concentrations were primarily associated with lipids or apolipoprotein concentrations in intermediate-to-low density lipoprotein (IDL + LDL) and high-density lipoprotein (HDL) that contain apoC-III. Comparing the highest and lowest tertiles of PFOA, the least-square means (SE) (mg/dl) were 4.16 -0.4 vs 3.47 -0.4 for apoB (P trend = 0.04), 2.03 -0.2 vs 1.66 -0.2 for apoC-III (P trend = 0.04), and 8.4 -0.8 vs 6.8 -0.8 for triglycerides (P trend = 0.03) in IDL + LDL fraction that contains apoC-III. For HDL that contains apoC-III, comparing the highest and lowest tertiles of PFOA, the least-square means (SE) (mg/dl) of apoC-III were 11.9 -0.7 vs 10.4 -0.7 (P trend = 0.01). In addition, elevated PFNA and PFDA concentrations were also significantly associated with higher concentrations of apoE in HDL that contains apoC-III (P trend< 0.01). Similar patterns of associations were demonstrated between baseline PFAS concentrations and lipoprotein subspecies measured at 2 years. Baseline PFAS levels were not associated with changes in lipoprotein subspecies during the intervention.CONCLUSIONS: Our results suggest that plasma PFAS concentrations are primarily associated with blood lipids and apolipoproteins in subspecies of IDL, LDL, and HDL that contain apoC-III, which are associated with elevated cardiovascular risk in epidemiological studies. Future studies of PFAS-associated cardiovascular risk should focus on lipid subfractions.	●									-		B	B
810	ヒト（代謝）	Liu, H. S.; Wen, L. L.; Chu, P. L.; Lin, C. Y.	Association among total serum isomers of perfluorinated chemicals, glucose homeostasis, lipid profiles, serum protein and metabolic syndrome in adults: NHANES, 2013-2014	2018	Environ Pollut. 018 Jan;232:73-79. doi: 10.1016/j.envpol.2017.09.019. Epub 2017 Sep 15.	Perfluorinated chemicals (PFCs) have been used widely in consumer products manufacture. Recent in vitro as well as animal studies have found that there are different toxicity and pharmacokinetic profiles between isomers of perfluorooctanoic acid (PFOA) and/or perfluorooctane sulfonate (PFOS). However, the differential effects of linear or branched PFOA/PFOS isomers on human beings have never been reported. Herein, we examined 1871 adult subjects (age older than 18 years) from the National Health and Nutrition Examination Survey (NHANES) 2013-2014 to determine the association between the isomers of PFOA/PFOS and serum biochemistry profiles, including glucose, lipids, protein and components of metabolic syndrome (MS). The results showed that for PFOA, increased linear PFOA was associated with increases in total cholesterol, serum albumin and an enhancement of β cell function as well as a decrease in the serum globulin. Increased branched PFOA was significantly associated with increased fasting glucose. All isomers of PFOA were positively associated with high-density lipoprotein-cholesterol (HDL-C) and negatively associated with glycohemoglobin (HbA1C). The branched PFOS was positively associated with β cell function and inversely associated with serum globulin. Both linear and branched isomers of PFOS were positively associated with the total protein and albumin. The increased branched PFOA was associated with less HDL-C insufficiency defined by the National Cholesterol Education Program Third Adult Treatment Panel (NCEP-ATP III) MS criteria, whereas the increased concentrations of serum total and linear PFOS were associated with less hypertriglyceridemia by the NCEP-ATP III. In conclusion, serum isomers of PFOA and PFOS were associated with glucose homeostasis, serum protein as well as lipid profiles; they were also indicators of MS. This may suggest that there is a distinct difference in the toxicokinetics of the isomers of PFOA and PFOS. Further clinical and animal studies are warranted to clarify the putative causal relationships between isomers and biochemical alterations.	●	●		●						-	1	B	A
811	ヒト（代謝）	Liu, X.; Zhang, L.; Chen, L.; Li, J.; Wang, Y.; Wang, J.; Meng, G.; Chi, M.; Zhao, Y.; Chen, H.; Wu, Y.	Structure-based investigation on the association between perfluoroalkyl acids exposure and both gestational diabetes mellitus and glucose homeostasis in pregnant women	2019	Environ Int. 2019 Jun;127:85-93. doi: 10.1016/j.envint.2019.03.035. Epub 2019 Mar 23.	Background: Biomonitoring studies have shown the presence of structurally diverse perfluoroalkyl acids (PFAAs) in humans but only a few studies are available regarding the differential structural effects of PFAAs on human health. Objective: The specific association between different structural PFAAs and both gestational diabetes mellitus (GDM) and glucose homeostasis in pregnant women was investigated. Methods: A prospective nested case-control study including 439 women was conducted during 2013-2015 in Beijing, China. First trimester maternal serum was collected and analyzed for 25 diverse PFAAs with varying carbon chain lengths, linear/branched isomers and carboxylate or sulfonate functional groups. The analyzed PFAAs were grouped into different exposure variables depending on structure characteristics. GDM cases were diagnosed at 24-28 weeks of gestation and individually matched in a 1:2 ratio to controls. Conditional logistic and linear regression was used to evaluate the association between structurally grouped PFAAs and both GDM risk and glucose homeostasis parameters. Results: Among the 25 PFAAs, 12 perfluoroalkyl carboxylates (PFCAs) and 8 perfluoroalkyl sulfonates (PFSAs) were detected in >55.0% of samples and were respectively grouped into different structural groups. The structural-based effect was observed for PFCAs, where short-chain (C4-C7) PFCAs continuous level was significantly associated with GDM with an estimated odds ratio (OR) of 1.99 (95% CI: 1.29, 3.09), and the multivariable-adjusted ORs (95% CI) of GDM for increasing tertiles of short-chain PFCAs were 1.00 (ref.), 1.82 (0.80, 4.16) and 3.01 (1.31, 6.94), P trend = 0.011. Additionally, increased concentration of short-chain PFCAs was significantly associated with higher postprandial glucose levels (P < 0.05). Non-significant association was observed between structure grouped PFSAs and GDM as well as glucose homeostasis. Conclusion: This investigation suggests a structure-specific association between short-chain PFCAs exposure and both GDM risk and impaired glucose homeostasis in pregnant women. These findings warrant further investigation with larger samples and a wide range of short-chain PFCAs exposure.	●	●								-		B	B
812	ヒト（代謝）	Macneil, J.; Steenland, N. K.; Shankar, A.; Ducatman, A.	A cross-sectional analysis of type II diabetes in a community with exposure to perfluorooctanoic acid (PFOA)	2009	Environ Res. 2009 Nov;109(8):997-1003. doi: 10.1016/j.envres.2009.08.002. Epub 2009 Sep 8.	BACKGROUND: Increased diabetes mortality has been reported in workers exposed to perfluorooctanoic acid (PFOA). We analyzed the relationships among serum PFOA, type II diabetes, and fasting glucose in a population with high levels of serum PFOA resulting from drinking contaminated water.METHODS: The study population was adults participating in a health survey in 2005-2006 (N=54,468). Subjects reported prevalent diabetes, age at diagnosis, and provided blood in which serum PFOA and glucose levels were measured. We conducted a case-control analysis restricted to long-time residents (> or 20 years, N=13,922), to maximize the likelihood that serum PFOA levels in 2005 reflected previous exposure. Cases (N=1055) were restricted to those with medical record validation and at least 10-year residence prior to diagnosis. We also studied fasting glucose and serum PFOA in a subset (N=21,642).RESULTS: Median serum PFOA was 28 ng/ml, compared with 4 ng/ml in the general US population. Reported diabetes prevalence was 7.8%, similar to what was expected. Adjusted for confounders, all upper deciles of serum PFOA had a decreased risk of diabetes compared with the lowest (odds ratios-ORs by decile, 1.00, 0.71, 0.60, 0.72, 0.65, 0.65, 0.87, 0.58, 0.62, 0.72). There was no consistent pattern between fasting serum glucose and PFOA (glucose by decile, 94, 95, 95, 93, 94, 92, 92, 92, 92, 93, adjusted for confounders).CONCLUSIONS: Our findings do not demonstrate an association between PFOA and either type II diabetes or fasting glucose level. Our data are limited by their cross-sectional nature, and do not preclude the possibility of a causal relationship.	●	●		●		●				-		C	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ラン①抽出	文献ラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
813	ヒト（代謝）	Mancini, F. R.; Rajaobelina, K.; Praud, D.; Dow, C.; Antignac, J. P.; Kvaskoff, M.; Severi, G.; Bonnet, F.; Boutron-Ruault, M. C.; Fagherazzi, G.	Nonlinear associations between dietary exposures to perfluorooctanoic acid (PFOA) or perfluorooctane sulfonate (PFOS) and type 2 diabetes risk in women: Findings from the E3N cohort study	2018	Int J Hyg Environ Health. 2018 Aug;221(7):1054-1060. doi: 10.1016/j.ijheh.2018.07.007. Epub 2018 Jul 25.	The incidence of type 2 diabetes (T2D) is steadily rising worldwide since the past 30 years. There is increasing interest in understanding the contribution of exposure to endocrine disrupting chemicals (EDCs) to T2D trend. Perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) are stable, persistent, and bioaccumulative synthetic compounds, suspected to act as EDCs and for which the diet is the main route of exposure. We investigated associations between estimated dietary exposure to PFOS and PFOA and the risk of T2D in the large E3N prospective cohort study. Among 71 270 women included in this study, 2680 cases of incident type 2 diabetes were validated during follow-up (1993-2012). Dietary exposure was estimated combining dietary consumption data collected in E3N and food contamination data provided by ANSES in the 2nd French Total Diet Study. The estimated mean dietary exposure to PFOS and PFOA was 0.50 ng/kg body weight/day and 0.86 ng/kg body weight/day respectively. An inverse U-shape association was found when considering PFOA and T2D: women in the 4th, 5th, and 6th decile groups had a HR [95%CI] of 1.21 [1.06-1.46], 1.35 [1.15-1.59], and 1.33 [1.05-1.41], respectively, when compared to women of the 1st decile group, while the other decile groups were not associated to the risk of T2D. The positive association had the strongest effect size for non-obese women (body mass index (BMI) ≤25 kg/m2). No association was found between dietary exposure to PFOS and T2D, except when considering only women with BMI≤25 kg/m2, in which a positive nonlinear association was observed (HR [95%CI] = 1.46 [1.09-1.96], 1.52 [1.09-2.11], and 1.44 [1.01-2.06] for the 6th, 8th, and 9th decile groups respectively). This is the first study to evaluate the association between dietary exposure to PFOA and PFOS and the risk of developing T2D in a large observational study with over 15 years of follow-up. The present study highlights the importance of studying the effects of EDCs in large epidemiological studies including not occupationally exposed populations, as well as the importance of considering exposure to PFOS and PFOA as a relevant risk factor for T2D.	●	●								-	1	B	A
814	ヒト（代謝）	Marks, K. J.; Jeddy, Z.; Flanders, W. D.; Northstone, K.; Fraser, A.; Calafat, A. M.; Kato, K.; Hartman, T. J.	Maternal serum concentrations of perfluoroalkyl substances during pregnancy and gestational weight gain: The Avon Longitudinal Study of Parents and Children	2019	Reprod Toxicol. 2019 Dec;90:8-14. doi: 10.1016/j.reprotox.2019.08.003. Epub 2019 Aug 12.	Perfluoroalkyl substances (PFAS) are chemicals used in the manufacture of consumer products. PFAS may act as endocrine disruptors, influencing metabolic pathways and weight-related outcomes. We analyzed associations of maternal serum pregnancy concentrations of PFAS with gestational weight gain (GWG). We used data from 905 women in a subsample of the Avon Longitudinal Study of Parents and Children. Women were routinely weighed in antenatal check-ups; absolute GWG was determined by subtracting the first weight measurement from the last. Linear regression was used to explore associations of maternal PFAS concentrations with absolute GWG, stratified by pre-pregnancy body mass index. Associations of maternal PFAS concentrations with absolute GWG were null. Ten percent higher perfluorooctane sulfonic acid (PFOS) was associated with GWG of -0.03kg (95% CI: -0.11, 0.06) and -0.12kg (95% CI: -0.30, 0.06) among under-/normal weight and overweight/obese mothers, respectively. Overall, findings suggest no association between maternal PFAS concentrations and GWG.	●	●								-		C	B
815	ヒト（代謝）	Martinsson, M.; Nielsen, C.; Björk, J.; Rylander, L.; Malmqvist, E.; Lindh, C.; Rignell-Hydbom, A.	Intrauterine exposure to perfluorinated compounds and overweight at age 4: A case-control study	2020	PLoS ONE. 2020 Mar 16;15(3):e0230137. doi: 10.1371/journal.pone.0230137. eCollection 2020.	AIMS: The aims were to investigate the association between maternal serum levels of perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), perfluorohexane sulfonate (PFHxS) and perfluorononanoic acid (PFNA) in early pregnancy and overweight in the child at 4 years and to assess potential heterogeneity in exposure effect between strata with different levels of other risk factors for overweight	●	●								-		D	B
816	ヒト（代謝）	Matilla-Santander, N.; Valvi, D.; Lopez-Espinosa, M. J.; Manzano-Salgado, C. B.; Ballester, F.; Ibarluzea, J.; Santa-Marina, L.; Schettgen, T.; Guxens, M.; Sunyer, J.; Vrijheid, M.	Exposure to Perfluoroalkyl Substances and Metabolic Outcomes in Pregnant Women: Evidence from the Spanish INMA Birth Cohorts	2017	Environ Health Perspect. 2017 Nov 13;125(11):117004. doi: 10.1289/EHP1062.	BACKGROUND: Exposure to perfluoroalkyl substances (PFASs) may increase risk for metabolic diseases; however, epidemiologic evidence is lacking at the present time. Pregnancy is a period of enhanced tissue plasticity for the fetus and the mother and may be a critical window of PFAS exposure susceptibility.OBJECTIVE: We evaluated the associations between PFAS exposures and metabolic outcomes in pregnant women.METHODS: We analyzed 1240 pregnant women from the Spanish INMA [Environment and Childhood Project (INfancia y Medio Ambiente)] birth cohort study (recruitment period: 2003-2008) with measured first pregnancy trimester plasma concentrations of four PFASs (in nanograms/milliliter). We used logistic regression models to estimate associations of PFASs (log10-transformed and categorized into quartiles) with impaired glucose tolerance (IGT) and gestational diabetes mellitus (GDM), and we used linear regression models to estimate associations with first-trimester serum levels of triglycerides, total cholesterol, and C-reactive protein (CRP).RESULTS: Perfluorooctane sulfonate (PFOS) and perfluorohexane sulfonate (PFHxS) were positively associated with IGT (137 cases) [OR per log10-unit increase=1.99 (95% CI: 1.06, 3.78) and OR=1.65 (0.95 CI: 0.99, 2.76), respectively]. PFOS and PFHxS associations with GDM (53 cases) were in a similar direction, but less precise. PFOS and perfluorononanoate (PFNA) were negatively associated with triglyceride levels [percent median change per log10-unit increase=-5.86% (95% CI: -9.91%, -1.63%) and percent median change per log10-unit increase=-4.75% (95% CI: -8.16%, -0.61%, respectively], whereas perfluorooctanoate (PFOA) was positively associated with total cholesterol [percent median change per log10-unit increase=1.26% (95% CI: 0.01%, 2.54%)]. PFASs were not associated with CRP in the subset of the population with available data (n=640).CONCLUSIONS: Although further confirmation is required, the findings from this study suggest that PFAS exposures during pregnancy may influence lipid metabolism and glucose tolerance and thus may impact the health of the mother and her child.	●	●								-	1	A	A
817	ヒト（代謝）	Mora, A. M.; Fleisch, A. F.; Rifas-Shiman, S. L.; Woo Baidal, J. A.; Pardo, L.; Webster, T. F.; Calafat, A. M.; Ye, X.; Oken, E.; Sagiv, S. K.	Early life exposure to per- and polyfluoroalkyl substances and mid-childhood lipid and alanine aminotransferase levels	2018	Environ Int. 2018 Feb;111:1-13. doi: 10.1016/j.envint.2017.11.008. Epub 2017 Nov 20.	BACKGROUND: Growing evidence suggests that exposure to per- and polyfluoroalkyl substances (PFASs) may disrupt lipid homeostasis and liver function, but data in children are limited.OBJECTIVE: We examined the association of prenatal and mid-childhood PFAS exposure with lipids and alanine aminotransferase (ALT) levels in children.METHODS: We studied 682 mother-child pairs from a Boston-area pre-birth cohort. We quantified PFASs in maternal plasma collected in pregnancy (median 9.7weeks gestation, 1999-2002) and in child plasma collected in mid-childhood (median age 7.7years, 2007-2010). In mid-childhood we also measured fasting total (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and ALT. We then derived low-density lipoprotein cholesterol (LDL-C) from TC, HDL-C, and TG using the Friedewald formula.RESULTS: Median (interquartile range, IQR) perfluorooctane sulfonate (PFOS), perfluorooctanoate (PFOA), and perfluorodecanoate (PFDeA) concentrations in child plasma were 6.2 (5.5), 4.3 (3.0), and 0.3 -0.3 ng/mL, respectively. Among girls, higher child PFOS, PFOA, and PFDeA concentrations were associated with detrimental changes in the lipid profile, including higher TC and/or LDL-C [e.g., β per IQR increment in PFOS=4.0mg/dL (95% CI: 0.3, 7.8) for TC and 2.6mg/dL (-0.5, 5.8) for LDL-C]. However, among both boys and girls, higher plasma concentrations of these child PFASs were also associated with higher HDL-C, which predicts better cardiovascular health, and slightly lower ALT, which may indicate better liver function. Prenatal PFAS concentrations were also modestly associated with improved childhood lipid and ALT levels.CONCLUSIONS: Our data suggest that prenatal and mid-childhood PFAS exposure may be associated with modest, but somewhat conflicting changes in the lipid profile and ALT levels in children.	●	●								-		B	B
818	ヒト（代謝）	Mora, S.	Nonfasting for Routine Lipid Testing: From Evidence to Action	2016	JAMA Intern Med 176: 1005-1006. doi: 10.1001/jamainternmed.2016.1979.	Relevant English-language peer-reviewed studies were identified through a literature search of MEDLINE and specific health economic journals through 2016 Bibliographies from these references as well as meta-analyses and applicable guideline statements were also reviewed.	●	●								-		C	C
819	ヒト（代謝）	Nelson, J. W.; Hatch, E. E.; Webster, T. F.	Exposure to Polyfluoroalkyl Chemicals and Cholesterol, Body Weight, and Insulin Resistance in the General US Population	2010	Environ Health Perspect. 2010 Feb;118(2):197-202. doi: 10.1289/ehp.0901165.	BACKGROUND: Polyfluoroalkyl chemicals (PFCs) are used commonly in commercial applications and are detected in humans and the environment worldwide. Concern has been raised that they may disrupt lipid and weight regulation.OBJECTIVES: We investigated the relationship between PFC serum concentrations and lipid and weight outcomes in a large publicly available data set.METHODS: We analyzed data from the 20032004 National Health and Nutrition Examination Survey (NHANES) for participants 1280 years of age. Using linear regression to control for covariates, we studied the association between serum concentrations of perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorooctane sulfonic acid (PFOS), and perfluorohexane sulfonic acid (PFHxS) and measures of cholesterol, body size, and insulin resistance.RESULTS: We observed a positive association between concentrations of PFOS, PFOA, and PFNA and total and non-high-density cholesterol. We found the opposite for PFHxS. Those in the highest quartile of PFOS exposure had total cholesterol levels 13.4 mg/dL [95% confidence interval (CI), 3.823.0] higher than those in the lowest quartile. For PFOA, PFNA, and PFHxS, effect estimates were 9.8 (95% CI, 0.2 to 19.7), 13.9 (95% CI, 1.925.9), and 7 (95% CI, 13.2 to 0.8), respectively. A similar pattern emerged when exposures were modeled continuously. We saw little evidence of a consistent association with body size or insulin resistance.CONCLUSIONS: This exploratory cross-sectional study is consistent with other epidemiologic studies in finding a positive association between PFOS and PFOA and cholesterol, despite much lower exposures in NHANES. Results for PFNA and PFHxS are novel, emphasizing the need to study PFCs other than PFOS and PFOA.	●	●	●	●	●	●	●			-	1	B	A

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
820	ヒト（代謝）	Nian, M.; Li, Q. Q.; Bloom, M.; Qian, Z. M.; Syberg, K. M.; Vaughn, M. G.; Wang, S. Q.; Wei, Q.; Zeeshan, M.; Gurram, N.; Chu, C.; Wang, J.; Tian, Y. P.; Hu, L. W.; Liu, K. K.; Yang, B. Y.; Liu, R. Q.; Feng, D.; Zeng, X. W.; Dong, G. H.	Liver function biomarkers disorder is associated with exposure to perfluoroalkyl acids in adults: Isomers of C8 Health Project in China	2019	Environ Res. 2019 May;172:81-88. doi: 10.1016/j.envres.2019.02.013. Epub 2019 Feb 11.	Exposure to chemicals may affect liver enzyme to increase the risk of liver diseases. Perfluoroalkyl acids (PFAAs) are one kind of persistent organic pollutants with hepatotoxic effect in organism. However, data is scarce to characterize the hepatotoxic effects of specific structural PFAA isomers in general population. To address this data gap, we evaluated the association between serum PFAAs concentration and liver function biomarkers in the Isomers of C8 Health Project in China. High performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) was used to measure 18 serum PFAAs, except for linear and branched isomers of PFOA/PFOS, nine perfluorinated carboxylic acids (PFCAs) and two perfluorinated sulfonic acids (PFSAs) were also included, in 1605 adult residents of Shenyang, China. Values for nine serum liver function biomarkers were determined by full-automatic blood biochemical analyzer. Linear regression was used to evaluate associations between PFAAs and continuous liver function biomarkers and logistic regression to assess markers dichotomized per clinical reference intervals. Results indicated that serum PFAAs concentrations were associated with liver biomarker levels suggestive of hepatotoxicity, especially for liver cell injury. For example, a 1 ln-unit increase in total-perfluorooctanoic acid (PFOA) exposure was associated with a 0.074 [95% confidence interval (CI): 3.9%, 11.0%] higher alanine aminotransferase (ALT) level in serum. Interestingly, we observed association between branched PFAA isomers and liver biomarkers. For example, one ln-unit increase in branched perfluorooctane sulfonate (PFOS) isomers exposure was associated with a 0.043 increase in ALT level (95% CI: 1.2%, 7.4%) and a 0.33 increased odds of having abnormal ALT (95% CI: 5.0%, 67.0%). Also, we found that PFNA had positive association with ALT [(6.2%, 0.95 CI: 3.1%, 9.4%) and AST levels (2.5%, 0.95 CI: 0.5%, 4.5%)]. Logistic regression results showed that PFPeA, PFHxA, PFNA, PFDoDA, PFTrDA and PFTeDA had statistically association with abnormal prealbumin. Conclusively, our results support previous studies showing association between PFAAs exposure and liver function biomarkers. We found new evidence that branched PFAAs isomer exposure is associated with the risk of clinically relevant hepatocellular dysfunction.	●	●	●							-		1	B	A
821	ヒト（代謝）	Pinney, S. M.; Windham, G. C.; Xie, C.; Herrick, R. L.; Calafat, A. M.; Mcwhorter, K.; Fassler, C. S.; Hiatt, R. A.; Kushi, L. H.; Biro, F. M.	Perfluorooctanoate and changes in anthropometric parameters with age in young girls in the Greater Cincinnati and San Francisco Bay Area	2019	Int J Hyg Environ Health. 2019 Aug;222(7):1038-1046. doi: 10.1016/j.ijheh.2019.07.002. Epub 2019 Jul 9.	Methods: We conducted a study of per- and polyfluoroalkyl substance biomarkers, including PFOA, in girls from Greater Cincinnati (CIN, N = 353) and the San Francisco Bay Area (SFBA, N = 351). PFOA was measured in the baseline serum sample collected in 2004-2007 of 704 girls at age 6-8 years. Mixed effects models were used to derive the effect of PFOA on BMI, waist-to-height and waist-to-hip ratios over increasing age in this longitudinal cohort. Results: Median PFOA serum concentrations were 7.3 (CIN) and 5.8 (SFBA) ng/mL, above the U.S. population median for children 12-19 years in 2005-2006 (3.8 ng/mL). Log-transformed serum PFOA had a strong inverse association with BMIz in the CIN girls (p = 0.0002) and the combined two-site data (p = 0.0008); the joint inverse effect of PFOA and Age*PFOA weakened at age at 10-11 years. However, in the SFBA group alone, the relationship was not significant (p = 0.1641) with no evidence of changing effect with age. The effect of PFOA on waist:height ratio was similar to BMIz at both sites, but we did not find a significant effect of PFOA on waist:hip ratio in either the CIN or SFBA girls. Conclusions: PFOA is associated with decreased BMI and waist:height ratio in young girls, but the strength of the relationship decreases with age. Site heterogeneity may be due to greater early life exposure in Cincinnati. Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. Use of trade names is for identification only and does not imply endorsement by the CDC, the Public Health Service, or the US Department of Health and Human Services.	●	●							-			B	B
822	ヒト（代謝）	Predieri, B.; Iughetti, L.; Guerranti, C.; Bruzzi, P.; Perra, G.; Focardi, S. E.	High Levels of Perfluorooctane Sulfonate in Children at the Onset of Diabetes	2015	International Journal of Endocrinology. 2015;2015:234358. doi: 10.1155/2015/234358. Epub 2015 May 5.	Background. Impairments of endocrine system may be associated with exposure to perfluorinated compounds that are able to bind nuclear receptors, including the peroxisome proliferator-activating receptors. Aim of this study was to assess perfluorooctane sulfonate and perfluorooctanoic acid concentrations in children and adolescents at the onset of type 1 diabetes compared to healthy controls. Methods. Forty-four children and adolescents were recruited and subdivided into two groups: (A) 25 subjects with type 1 diabetes and (B) 19 healthy controls. Perfluorinated compounds were measured using high performance liquid chromatography with electrospray ionization tandem mass spectrometry. Nonparametric statistical analysis was performed. Results. Perfluorooctane sulfonate concentrations were significantly higher in patients with type 1 diabetes compared to controls (1.53 ± 1.5 versus 0.55 ± 0.15 ng/mL, resp.; p < 0.001). Multivariate linear regression analysis identified lipid levels as significant predictive factors for perfluorooctane sulfonate levels. Conclusions. Our data suggests that higher serum levels of perfluorooctane sulfonate may be considered a biomarker of exposure and susceptibility to develop type 1 diabetes.	●	●		●						-			C	C
823	ヒト（代謝）	823__Preston, E. V.; Rifas-Shiman, S. L.; Hivert, M. F.; Zota, A. R.; Sagiv, S. K.; Calafat, A. M.; Oken, E.; James-Todd, T.	Associations of per- and polyfluoroalkyl substances (PFAS) with glucose tolerance during pregnancy in project viva	2020	J Clin Endocrinol Metab. 2020 Aug 1;105(8):e2864-e2876. doi: 10.1210/clinem/dgaa328.	Per- and polyfluoroalkyl substances (PFAS) exposure may alter glucose homeostasis. Research on PFAS exposure and glucose tolerance during pregnancy is limited.	●	●							-			D	D
824	ヒト（代謝）	Rahman, M. L.; Zhang, C.; Smarr, M. M.; Lee, S.; Honda, M.; Kannan, K.; Tekola-Ayele, F.; Buck Louis, G. M.	Persistent organic pollutants and gestational diabetes: A multi-center prospective cohort study of healthy US women	2019	Environ Int. 2019 Mar;124:249-258. doi: 10.1016/j.envint.2019.01.027. Epub 2019 Jan 16.	BACKGROUND: Persistent organic pollutants (POPs) are linked with insulin resistance and type-2 diabetes (T2D) in the general population. However, their associations with gestational diabetes (GDM) are inconsistent.	●	●							-			D	D
825	ヒト（代謝）	Ren, Y.; Jin, L.; Yang, F.; Liang, H.; Zhang, Z.; Du, J.; Song, X.; Miao, M.; Yuan, W.	Concentrations of perfluoroalkyl and polyfluoroalkyl substances and blood glucose in pregnant women	2020	Environ Health. 2020 Aug 17;19(1):88. doi: 10.1186/s12940-020-00640-8.	Evidence on the association between exposure to perfluoroalkyl and polyfluoroalkyl substances (PFASs) and blood glucose concentrations in pregnant women is inconsistent. This study aimed to examine the association between PFAS exposure and the concentrations of fasting plasma glucose (FPG) and one-hour plasma glucose (1 h-PG) after a 50-g oral glucose tolerance test in pregnant women.	●	●							-			D	D
826	ヒト（代謝）	Sakr, C. J.; Kreckmann, K. H.; Green, J. W.; Gillies, P. J.; Reynolds, J. L.; Leonard, R. C.	Cross-sectional study of lipids and liver enzymes related to a serum biomarker of exposure (ammonia perfluorooctanoate or APFO) as part of a general health survey in a cohorent of occupational exposed workers	2007	J Occup Environ Med. 2007 Oct;49(10):1086-96. doi: 10.1097/JOM.0b013e318156eca3.	OBJECTIVE: To examine the relationship between serum perfluorooctanoate (PFOA), a biomarker of ammonium perfluorooctanoate (APFO) exposure, and lipids and liver enzymes in a cross-sectional study among workers with potential occupational exposure to APFO.	●	●		●		●	●			-			D	C
827	ヒト（代謝）	Salihovic, S.; Stubleski, J.; Kärrman, A.; Larsson, A.; Fall, T.; Lind, L.; Lind, P. M.	Changes in markers of liver function in relation to changes in perfluoroalkyl substances - A longitudinal study	2018	Environ Int. 2018 Aug;117:196-203. doi: 10.1016/j.envint.2018.04.052. Epub 2018 May 10.	BACKGROUND: While it is known that perfluoroalkyl substances (PFASs) induce liver toxicity in experimental studies, the evidence of an association in humans is inconsistent.OBJECTIVE: The main aim of the present study was to examine the association of PFAS concentrations and markers of liver function using panel data.METHODS: We investigated 1002 individuals from Sweden (50% women) at ages 70, 75 and 80 in 2001-2014. Eight PFASs were measured in plasma using isotope dilution ultra-performance liquid chromatography/tandem mass spectrometry (UPLC-MS/MS). Bilirubin and hepatic enzymes alanine aminotransferase (ALT), alkaline phosphatase (ALP), and γ-glutamyltransferase (GGT) were determined in serum using an immunoassay methodology. Mixed-effects linear regression models were used to examine the relationship between the changes in markers of liver function and changes in PFAS levels.RESULTS: The changes in majority of PFAS concentrations were positively associated with the changes in activity of ALT, ALP, and GGT and inversely associated with the changes in circulating bilirubin after adjustment for gender and the time-updated covariates LDL- and HDL-cholesterol, serum triglycerides, BMI, statin use, smoking, fasting glucose levels and correction for multiple testing. For example, changes in perfluorononanoic acid (PFNA) were associated with the changes liver function markers βBILIRUBIN = -1.56, 0.95 confidence interval (CI) -1.93 to -1.19, βALT = 0.04, 0.95 CI 0.03-0.06, and βALP = 0.11, 0.95 CI 0.06-0.15.CONCLUSION: Our longitudinal assessment established associations between changes in markers of liver function and changes in plasma PFAS concentrations. These findings suggest a relationship between low-dose background PFAS exposure and altered liver function in the general population.	●	●	●							-			B	B
828	ヒト（代謝）	Seo, S. H.; Son, M. H.; Choi, S. D.; Lee, D. H.; Chang, Y. S.	Influence of exposure to perfluoroalkyl substances (PFASs) on the Korean general population: 10-year trend and health effects	2018	Environ Int. 2018 Apr;113:149-161. doi: 10.1016/j.envint.2018.01.025. Epub 2018 Feb 6.	This study demonstrated the 10-year trend of 13 perfluoroalkyl substances (PFASs) serum levels among 786 adults living in Seoul, Korea. PFAS levels gradually increased from 2006 to 2013, decreasing thereafter. We found that PFAS levels were higher in male than in female participants and were positively correlated with age. PFASs were not significantly correlated with body mass index, although we observed positive correlations with total cholesterol, low-density lipoprotein cholesterol, and triglycerides and negative correlations with high-density lipoprotein cholesterol. Uric acid and free thyroxine (fT4) also showed positive correlations with major congeners while correlations between thyroid stimulating hormone and PFASs were inconsistent. We demonstrated significant correlations between fT4 and perfluorononanoic acid (PFNA), perfluorohexane sulfonate (PFHxS), and perfluorodecanoic acid (PFDA). There were significant differences in PFHxS and perfluorododecanoic acid (PFDoDA) levels between participants with and without diabetes. Furthermore, principal component analysis suggested possible differences in disease manifestation based on the congener distribution of PFASs. This study is the first study of temporal trends of 13 PFAS congeners in serum samples obtained from the Korean general population; it is currently longest and largest scale study of this type.	●	●	●							-			B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
829	ヒト（代謝）	Shapiro, G. D.; Dodds, L.; Arbuckle, T. E.; Ashley-Martin, J.; Ettinger, A. S.; Fisher, M.; Taback, S.; Bouchard, M. F.; Monnier, P.; Dallaire, R.; Morisset, A. S.; Fraser, W.	Exposure to organophosphorus and organochlorine pesticides, perfluoroalkyl substances, and polychlorinated biphenyls in pregnancy and the association with impaired glucose tolerance and gestational diabetes mellitus: The MIREC Study	2016	Environ Res. 2016 May;147:71-81. doi: 10.1016/j.envres.2016.01.040. Epub 2016 Feb 5.	BACKGROUND: Studies report increases in rates of gestational diabetes mellitus (GDM) over recent decades. Environmental chemicals may increase the risk of diabetes through impacts on glucose metabolism, mitochondrial dysfunction, and endocrine-disrupting mechanisms including effects on pancreatic β-cell function and adiponectin release.OBJECTIVES: To determine the associations between pesticides, perfluoroalkyl substances (PFASs) and polychlorinated biphenyls (PCBs) measured in early pregnancy and impaired glucose tolerance (IGT) and GDM in a Canadian birth cohort.METHODS: Women enrolled in the Maternal-Infant Research on Environmental Chemicals (MIREC) Study were included if they had a singleton delivery and did not have pre-existing diabetes. Exposure variables included three organophosphorus (OP) pesticide metabolites detected in first-trimester urine samples, as well as three organochlorine (OC) pesticides, three PFASs, and four PCBs in first-trimester blood samples. Gestational IGT and GDM were assessed by chart review in accordance with published guidelines. Adjusted logistic regression models were used to calculate odds ratios (ORs) and 0.95 confidence intervals (CI) for the association between quartiles of environmental chemicals and both gestational IGT and GDM.RESULTS: Of the 2001 women recruited into the MIREC cohort, 1274 met the inclusion criteria and had outcome and biomonitoring data available. Significantly lower odds of GDM were observed in the third and fourth quartiles of dimethylphosphate (DMP) and in the fourth quartile of dimethylthiophosphate (DMTP) in adjusted analyses (DMP Q3: OR=0.2, 0.95 CI=0.1-0.7; DMP Q4: OR=0.3, 0.95 CI=0.1-0.8; DMTP: OR=0.3, 0.95 CI=0.1-0.9). Significantly elevated odds of gestational IGT was observed in the second quartile of perfluorohexane sulfonate (PFHxS) (OR=3.5, 0.95 CI=1.4-8.9). No evidence of associations with GDM or IGT during pregnancy was observed for PCBs or OC pesticides.CONCLUSIONS: We did not find consistent evidence for any positive associations between the chemicals we examined and GDM or IGT during pregnancy. We observed statistical evidence of inverse relationships between urine concentrations of DMP and DMTP with GDM. We cannot rule out the influence of residual confounding due to unmeasured protective factors, such as nutritional benefits from fruit and vegetable consumption, also associated with pesticide exposure, on the observed inverse associations between maternal OP pesticide metabolites and GDM. These findings require further investigation.	●	●	●	●						-		C	C
830	ヒト（代謝）	Skuladottir, M.; Ramel, A.; Rytter, D.; Haug, L. S.; Sabaredzovic, A.; Bech, B. H.; Henriksen, T. B.; Olsen, S. F.; Halldorsson, T. I.	Examining confounding by diet in the association between perfluoroalkyl acids and serum cholesterol in pregnancy	2015	Environ Res. 2015 Nov;143(Pt A):33-8. doi: 10.1016/j.envres.2015.09.001. Epub 2015 Sep 30.	BACKGROUND: Perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) have consistently been associated with higher cholesterol levels in cross sectional studies. Concerns have, however, been raised about potential confounding by diet and clinical relevance.OBJECTIVE: To examine the association between concentrations of PFOS and PFOA and total cholesterol in serum during pregnancy taking into considerations confounding by diet.METHODS: 854 Danish women who gave birth in 1988-89 and provided a blood sample and reported their diet in week 30 of gestation.RESULTS: Mean serum PFOS, PFOA and total cholesterol concentrations were 22.3 ng/mL, 4.1 ng/mL and 7.3 mmol/L, respectively. Maternal diet was a significant predictor of serum PFOS and PFOA concentrations. In particular intake of meat and meat products was positively associated while intake of vegetables was inversely associated (P for trend <0.01) with relative difference between the highest and lowest quartile in PFOS and PFOA concentrations ranging between 0.06 and 0.25 of mean values. After adjustment for dietary factors both PFOA and PFOS were positively and similarly associated with serum cholesterol (P for trend ≤0.01). For example, the mean increase in serum cholesterol was 0.39 mmol/L (95%CI: 0.09, 0.68) when comparing women in the highest to lowest quintile of PFOA concentrations. In comparison the mean increase in serum cholesterol was 0.61 mmol/L (95%CI: 0.17, 1.05) when comparing women in the highest to lowest quintile of saturated fat intake.CONCLUSION: In this study associations between PFOS and PFOA with serum cholesterol appeared unrelated to dietary intake and were similar in magnitude as the associations between saturated fat intake and serum cholesterol.	●	●		●			●			-	1	B	A
831	ヒト（代謝）	Spratlen, M. J.; Perera, F. P.; Lederman, S. A.; Robinson, M.; Kannan, K.; Herbstman, J.; Trasande, L.	The association between perfluoroalkyl substances and lipids in cord blood	2020	J Clin Endocrinol Metab. 2020 Jan 1;105(1):43-54. doi: 10.1210/clinem/dgz024.	INTRODUCTION: Perfluoroalkyl substances (PFAS) were among various persistent organic pollutants suspected to have been released during the collapse of the World Trade Center (WTC) on 9/11. Evidence suggests PFAS may have cardiometabolic effects, including alterations in lipid profiles. This study evaluated the association between cord PFAS and lipids in a population prenatally exposed to the WTC disaster.STUDY POPULATION: 222 pregnant women in the Columbia University WTC birth cohort enrolled between December 13, 2001 and June 26, 2002 at hospitals located near the WTC site: Beth Israel, St. Vincent's, and New York University Downtown.METHODS: We evaluated the association between five cord blood PFAS (perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), perfluorohexanesulfonic acid (PFHxS), perfluorononanoic acid (PFNA), perfluorodecane sulfonate (PFDS)) and cord blood lipids (total lipids, total cholesterol, triglycerides).RESULTS: Median (interquartile range (IQR)) concentrations of PFAS were 6.32 (4.58-8.57), 2.46 (1.77, 3.24), 0.38 (0.25, 0.74), 0.66 (0.48, 0.95) and 0.11 (0.09, 0.16) ng/mL for PFOS, PFOA, PFNA, PFHxS and PFDS, respectively. Median (IQR) for lipids were 59 (51.5, 68.5) mg/dL for total cholesterol, 196.5 (170.5, 221.2) mg/dL for total lipids and 33.1 (24.2, 43.9) mg/dL for triglycerides. In fully adjusted models, several PFAS were associated with higher lipid levels, including evidence of a strong linear trend between triglycerides and both PFOA and PFHxS.CONCLUSIONS: Findings support previous evidence of an association between PFAS exposure and altered lipid profiles and add novel information on this relationship in cord blood, as well as for an understudied PFAS, PFDS.	●	●								-	1	A	B
832	ヒト（代謝）	Su, T. C.; Kuo, C. C.; Hwang, J. J.; Lien, G. W.; Chen, M. F.; Chen, P. C.	Serum perfluorinated chemicals, glucose homeostasis and the risk of diabetes in working-aged Taiwanese adults	2016	Environ Int. 2016 Mar;88:15-22. doi: 10.1016/j.envint.2015.11.016. Epub 2015 Dec 14.	BACKGROUND: The link among perfluoroalkyl and polyfluoroalkyl substances (PFASs), abnormal glucose homeostasis and the risk of diabetes has been intensively debated with conflicting evidence.OBJECTIVES: We evaluated the associations among PFASs, oral glucose tolerance testing (OGTT) curves and diabetes prevalence in 571 working-aged Taiwanese participants.METHODS: Exposure measures included serum perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorononanoic acid (PFNA), and perfluoroundecanoic acid (PFUA). Outcomes were OGTT curves and prevalent diabetes defined by fasting blood glucose (FBG) ≥126mg/dL, 2-h glucose ≥200mg/dL, or glycated hemoglobin ≥6.5%. Analyses were performed with multiple logistic regression and functional data analysis.RESULTS: A total of 39 participants -0.068 had diabetes in this study. After full adjustment, the increase in the geometric means of FBG, 2-h glucose concentrations, and area under the OGTT curve (AUC120) with a doubling increase in PFOS was 0.03 (95% CI 1-4), 0.08 (5-12), and 0.06 (4-9), respectively. Compared to the lowest-quartile of PFOS concentrations (<2.4ng/ml), the OGTT trajectories were significantly steeper in participants of the highest-quartile PFOS exposure (>4.8ng/ml) and the vertical shifting of the mean curve for each PFOS quartile showed a dose-response pattern. The adjusted odds ratio for diabetes comparing the highest to lowest quartile was 3.37 (95% CI 1.18-9.65). For PFOA, PFNA, and PFUA, the opposite pattern of OGTT trajectory and the opposite risk profile for diabetes were observed.CONCLUSIONS: Chronic PFOS exposure was associated with impaired glucose homeostasis and the increased prevalence of diabetes. However, PFOA, PFNA, and PFUA showed a potential protective effect against glucose intolerance and the risk of diabetes. Future research focusing on clarifying possible differential effects of different species of PFASs on glucose homeostasis and establishing the prospective associations between PFASs and diabetes is needed.	●	●	●	●						-		B	B
833	ヒト（代謝）	Sun, Q. et8; Zong, G.; Valvi, D.; Nielsen, F.; Coull, B.; Grandjean, P.	Plasma concentrations of perfluoroalkyl substances and risk of Type 2 diabetes: A prospective investigation among U	2018	Environ Health Perspect. 2018 Mar 1;126(3):037001. doi: 10.1289/EHP2619.	BACKGROUND: Emerging evidence suggests that perfluoroalkyl substances (PFASs) are endocrine disruptors and may contribute to the etiology of type 2 diabetes (T2D), but this hypothesis needs to be clarified in prospective human studies.OBJECTIVES: Our objective was to examine the associations between PFAS exposures and subsequent incidence of T2D in the Nurses' Health Study II (NHSII). In addition, we aimed to evaluate potential demographic and lifestyle determinants of plasma PFAS concentrations.METHODS: A prospective nested case-control study of T2D was conducted among participants who were free of diabetes, cardiovascular disease, and cancer in 1995-2000 [(mean±SD): 45.3±4.4y) of age]. We identified and ascertained 793 incident T2D cases through 2011 (mean±SD) years of follow-up: 6.7±3.7y). Each case was individually matched to a control (on age, month and fasting status at sample collection, and menopausal status and hormone replacement therapy). Plasma concentrations of five major PFASs, including perfluorooctanesulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorohexanesulfonate, perfluorononanoic acid, and perfluorodecanoic acid were measured. Odds ratios (ORs) of T2D by PFAS tertiles were estimated by conditional logistic regression.RESULTS: Shorter breastfeeding duration and higher intake of certain foods, such as seafood and popcorn, were significantly associated with higher plasma concentrations of PFASs among controls. After multivariate adjustment for T2D risk factors, including body mass index, family history, physical activity, and other covariates, higher plasma concentrations of PFOS and PFOA were associated with an elevated risk of T2D. Comparing extreme tertiles of PFOS or PFOA, ORs were 1.62 (95% CI: 1.09, 2.41; ptrend=0.02) and 1.54 (95% CI: 1.04, 2.28; ptrend=0.03), respectively. Other PFASs were not clearly associated with T2D risk.CONCLUSIONS: Background exposures to PFASs in the late 1990s were associated with higher T2D risk during the following years in a prospective case-control study of women from the NHSII. These findings support a potential diabetogenic effect of PFAS exposures.	●	●		●						-	1	A	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ランク①	文献ランク②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
834	ヒト（代謝）	Tian, Y. P.; Zeng, X. W.; Bloom, M. S.; Lin, S.; Wang, S. Q.; Yim, S. H. L.; Yang, M.; Chu, C.; Gurram, N.; Hu, L. W.; Liu, K. K.; Yang, B. Y.; Feng, D.; Liu, R. Q.; Nian, M.; Dong, G. H.	Isomers of perfluoroalkyl substances and overweight status among Chinese by sex status: Isomers of C8 Health Project in China	2019	Environ Int. 2019 Mar;124:130-138. doi: 10.1016/j.envint.2019.01.006. Epub 2019 Jan 11.	Previous investigations on the associations of polyfluoroalkyl substances (PFASs) with overweight/obesity are mixed. Moreover, little information has been reported about the association between isomers of PFASs with body mass index (BMI), waist circumference (WC) or overweight. To address this shortcoming in the literature, we conducted a study involving 1612 Chinese adults (1204 men and 408 women), ages 22-96 years old, from Shenyang, China, to analyze serum isomers of perfluorooctanesulfonate (PFOS), perfluorooctanoate (PFOA), and other PFASs. Height, weight and WC were measured by a standardized protocol of WHO. Results indicated that increased serum concentrations of all (both branched and linear) isomers of PFASs were associated with a higher prevalence of overweight, and these associations were more pronounced in women. The adjusted odds ratios (ORs) from logistic regression analyses among women were 1.45 (95% confidence interval [CI]: 1.06, 1.99) for linear PFOS isomers, 1.33 (95% CI: 1.00, 1.77) for branched PFOS isomers, 1.39 (95% CI: 1.06, 1.81) for 3 + 4 + 5m PFOS, 1.54 (95% CI: 1.08, 2.21) for linear PFOA isomers, and 1.62 (95% CI: 1.05, 2.51) for branched PFOA isomers, respectively. Associations with increased WC were yielded a similar pattern. Linear regression models also showed positive associations between PFASs and BMI or WC. In conclusion, this study suggests that PFASs and their isomers are positively associated with overweight or increased WC, and the associations are stronger in women. Furthermore, PFOA and its isomers displayed the most robust obesogenic associations.	●	●								-		B	B
835	ヒト（代謝）	Wang, H.; Yang, J.; Du, H.; Xu, L.; Liu, S.; Yi, J.; Qian, X.; Chen, Y.; Jiang, Q.; He, G.	Perfluoroalkyl substances, glucose homeostasis, and gestational diabetes mellitus in Chinese pregnant women: A repeat measurement-based prospective study	2018	Environ Int. 2018 May;114:12-20. doi: 10.1016/j.envint.2018.01.027. Epub 2018 Feb 20.	BACKGROUND: Exposure to perfluoroalkyl substances (PFASs) can affect glucose homeostasis and has been suggested as a potential risk of diabetes mellitus, but data are limited for pregnant women.OBJECTIVES: We aimed to explore the associations of exposure to PFASs with glucose homeostasis and gestational diabetes mellitus (GDM) in Chinese pregnant women.METHODS: The current study was conducted in Hebei Province of Northern China between 2013 and 2014 and 560 pregnant women were recruited in their early term of pregnancy and two representative serum PFASs, perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS), were measured. In 385 pregnant women who completed oral glucose tolerance test (OGTT), the associations of serum PFOA and PFOS concentrations with fasting blood glucose (FBG), fasting insulin (FIns), and homeostasis model assessment of insulin resistance (HOMA-IR) in the early, middle, and late terms of pregnancy and occurrence of GDM were examined using linear and Cox proportional hazard regression models. The reproducibility of serum PFASs during pregnancy was assessed in 230 pregnant women.RESULTS: The intraclass correlation coefficients of serum PFASs, covariates, and outcomes based on averaged repeat measurement (0.35-0.96) were higher than those based on single measurement (0.16-0.92). Serum PFOA was positively associated with averaged FIns and HOMA-IR in the early, middle, and late terms of pregnancy and averaged blood glucose level at 1 h and 2 h of OGTT, but serum PFOS tended to be negatively associated with averaged FBG and OGTT blood glucose. The adjusted hazard ratios of GDM associated with serum PFOA and PFOS were 1.98 (95% confidence interval: 0.70-5.57; p-value: 0.197) and 0.71 (0.29-1.75; 0.453), respectively.CONCLUSIONS: Our data raised a possibility that exposure to PFASs might have different influences on glucose homeostasis and GDM in Chinese pregnant women. More lab and human studies are needed to further test the hypothesis and investigate potential mechanisms.	●	●		●						-		B	B
836	ヒト（代謝）	Wang, J.; Zhang, Y.; Zhang, W.; Jin, Y.; Dai, J.	Association of perfluorooctanoic acid with HDL cholesterol and circulating miR-26b and miR-199-3p in workers of a fluorochemical plant and nearby residents	2012	Environ Sci Technol. 2012 Sep 4;46(17):9274-81. doi: 10.1021/es300906q. Epub 2012 Aug 21.	Perfluoroalkyl chemicals (PFCs) are stable man-made compounds with many industrial and commercial uses. Concern has been raised that they may exert deleterious effects, especially on lipid regulation. We aimed to assess exposure to perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), and seven other PFCs in occupational workers from a fluorochemical plant and nearby community residents, and to investigate the association between PFOA and serum biomarkers. Serum biomarkers included not only biochemical parameters, such as lipids and enzymes, but also circulating microRNAs (miRNAs). Samples were analyzed by high-pressure liquid chromatography/tandem mass spectrometry (HPLC-MS/MS). Circulating miRNA levels were detected by quantitative polymerase chain reaction (PCR). Analyses were conducted by correlation and linear regression. We detected PFOS, PFOA, perfluorohexane sulfonate (PFHxS), perfluorononanoic acid (PFNA), and perfluorodecanoic acid (PFDA) in all samples. The median levels of serum PFOA and PFOS were 284.34 ng/mL and 34.16 ng/mL in residents and 1635.96 ng/mL and 33.46 ng/mL in occupational participants, respectively. To our knowledge, we found for the first time that PFOA was negatively associated with high-density lipoprotein cholesterol (HDL-C) in workers using linear regression after adjusting for potential confounders. Circulating miR-26b and miR-199a-3p were elevated with serum concentration of PFOA. Although the limitations of small sample size and the cross-sectional nature of the current study constrained causal inferences, the observed associations between PFOA and these serum biomarkers warrant further study.	●	●		●			●			-		B	B
837	ヒト（代謝）	Wang, Y.; Zhang, L.; Teng, Y.; Zhang, J.; Yang, L.; Li, J.; Lai, J.; Zhao, Y.; Wu, Y.	Association of serum levels of perfluoroalkyl substances with gestational diabetes mellitus and postpartum blood glucose	2018	J Environ Sci (China). 2018 Jul;69:5-11. doi: 10.1016/j.jes.2018.03.016. Epub 2018 Mar 22.	This study was conducted to examine the association of perfluoroalkyl substance (PFAS) exposure with gestational diabetes mellitus (GDM) risk and postpartum fasting blood glucose. We used a 0.0430555555555556 matched case-control study with 84 GDM subjects and 168 healthy pregnant women from Beijing, China. The maternal blood was collected at 1-2days before delivery, and eight linear isomers and fourteen branched isomers were determined in maternal serum. Logistic regression analyses were performed to evaluate the associations after adjusting for potential confounders. The median of the sum of levels of total PFASs was 4.24ng/mL with a interquartile range (IQR) of 2.82-6.54ng/mL. Although maternal PFAS exposure was not associated with risk of GDM, significant positive associations were observed between evaluated exposure to specific PFAS congeners and increasing blood glucose. The odds ratio (ORs) of the highest category of postpartum fasting blood glucose for perfluoro-1-metylheptylsulfonat (1m-PFOS), perfluoro-3/4-metylheptylsulfonat (3m+4m-PFOS), perfluoro-5-metylheptylsulfonat (5m-PFOS), and perfluorohexane sulfonate (PFHxS) were 2.03 (95% CI: 1.09-3.77), 1.93 (95% CI: 1.04-3.58), 2.48 (95% CI: 1.33-4.65), and 2.26 (95% CI: 1.21-4.21), respectively, suggesting negative effects of maternal exposure to specific PFAS compounds on glucose metabolism.	●	●								-		B	B
838	ヒト（代謝）	Warembourg, C.; Maitre, L.,ea; Tamayo-Uria, I.; Fossati, S.; Roumeliotaki, T.; Aasvang, G. M.; Andrusaityte, S.; Casas, M.; Cequier, E.; Chatzi, L.; Dedele, A.; Gonzalez, , J. R.; Grazuleviciene, R.; Haug, L. S.; Hernandez-Ferrer, C.; Heude, B.; Karachaliou, M.; Krog, N. H.; Mceachan, R.; Nieuwenhuijsen, M.; Petraviciene, I.; Quentin, J.; Robinson, O.; Sakhi, A. K.; Slama, R.; Thomsen, C.; Urquiza, J.; Vafeiadi, M.; West, J.; Wright, J.; Vrijheid, M.; Basagana, X.	Early-life environmental exposures and blood pressure in children	2019	J Am Coll Cardiol. 2019 Sep 10;74(10):1317-1328. doi: 10.1016/j.jacc.2019.06.069.	BACKGROUND: Growing evidence exists about the fetal and environmental origins of hypertension, but mainly limited to single-exposure studies. The exposome has been proposed as a more holistic approach by studying many exposures simultaneously.OBJECTIVES: This study aims to evaluate the association between a wide range of prenatal and postnatal exposures and blood pressure (BP) in children.METHODS: Systolic and diastolic BP were measured among 1277 children from the European HELIX (Human Early-Life Exposome) cohort aged 6 to 11 years. Prenatal (n = 89) and postnatal (n = 128) exposures include air pollution, built environment, meteorology, natural spaces, traffic, noise, chemicals, and lifestyles. Two methods adjusted for confounders were applied: an exposome-wide association study considering the exposures independently, and the deletion-substitution-addition algorithm considering all the exposures simultaneously.RESULTS: Decreases in systolic BP were observed with facility density (ß change for an interquartile-range increase in exposure: -1.7 mm Hg [95% confidence interval (CI): -2.5 to -0.8 mm Hg]), maternal concentrations of polychlorinated biphenyl 118 (-1.4 mm Hg [95% CI: -2.6 to -0.2 mm Hg]) and child concentrations of dichlorodiphenyldichloroethylene (DDE: -1.6 mm Hg [95% CI: -2.4 to -0.7 mm Hg]), hexachlorobenzene (-1.5 mm Hg [95% CI: -2.4 to -0.6 mm Hg]), and mono-benzyl phthalate (-0.7 mm Hg [95% CI: -1.3 to -0.1 mm Hg]), whereas increases in systolic BP were observed with outdoor temperature during pregnancy (1.6 mm Hg [95% CI: 0.2 to 2.9 mm Hg]), high fish intake during pregnancy (2.0 mm Hg [95% CI: 0.4 to 3.5 mm Hg]), maternal cotinine concentrations (1.2 mm Hg [95% CI: -0.3 to 2.8 mm Hg]), and child perfluorooctanoate concentrations (0.9 mm Hg [95% CI: 0.1 to 1.6 mm Hg]). Decreases in diastolic BP were observed with outdoor temperature at examination (-1.4 mm Hg [95% CI: -2.3 to -0.5 mm Hg]) and child DDE concentrations (-1.1 mm Hg [95% CI: -1.9 to -0.3 mm Hg]), whereas increases in diastolic BP were observed with maternal bisphenol-A concentrations (0.7 mm Hg [95% CI: 0.1 to 1.4 mm Hg]), high fish intake during pregnancy (1.2 mm Hg [95% CI: -0.2 to 2.7 mm Hg]), and child copper concentrations (0.9 mm Hg [95% CI: 0.3 to 1.6 mm Hg]).CONCLUSIONS: This study suggests that early-life exposure to several chemicals, as well as built environment and meteorological factors, may affect BP in children.	●	●								-		C	B
839	ヒト（代謝）	Xu, H.; Zhou, Q.; Zhang, J.; Chen, X.; Zhao, H.; Lu, H.; Ma, B.; Wang, Z.; Wu, C.; Ying, C.; Xiong, Y.; Zhou, Z.; Li, X.	Exposure to elevated per- and polyfluoroalkyl substances in early pregnancy is related to increased risk of gestational diabetes mellitus: A nested case-control study in Shanghai, China	2020	Environ Int. 2020 Oct;143:105952. doi: 10.1016/j.envint.2020.105952. Epub 2020 Jul 24.	Long-chain per- and polyfluoroalkyl substances (PFASs) and their short-chain alternatives have been produced and used extensively in China. However, it is unclear whether these compounds contribute to the risk of gestational diabetes mellitus (GDM) in women residing in contaminated areas.	●	●								-		D	C
840	ヒト（代謝）	Yang, Q.; Guo, X.; Sun, P.; Chen, Y.; Zhang, W.; Gao, A.	Association of serum levels of perfluoroalkyl substances (PFASs) with the metabolic syndrome (MetS) in Chinese male adults: A cross-sectional study	2018	Sci Total Environ. 2018 Apr 15;621:1542-1549. doi: 10.1016/j.scitotenv.2017.10.074. Epub 2017 Oct 18.	As extensively used chemicals in a variety of consumer products, perfluoroalkyl substances (PFASs) are ubiquitous and could bring significant risk to human health. However, the effect of PFASs on metabolic syndrome (MetS) is not fully understood. In 2015, a preliminary cross-sectional study was undertaken. A total of 148 male subjects including 81 affected by MetS and 67 non-MetS participants as the reference were recruited from Physical Examination Center affiliated to Capital Medical University, China. Serum levels of perfluorohexane sulfonic acid (PFHxS), perfluorooctanoic acid (PFOA) and perfluorononanoic acid (PFNA) were significantly higher in the subjects with MetS. Logistic regression results showed that concentration of PFNA in serum was associated with 10.9-fold [95% confidence interval (CI), 2.00-59.1] increased risk of MetS. Moreover, increased serum PFNA concentrations were associated with high blood pressure [both for systolic and diastolic blood pressure (SBP and DBP); odds ratio (OR) 7.52 (95%CI, 1.34-42.1) for SBP and 7.27 (95%CI, 1.17-45.1) for DBP], hypertriglyceridemia [13.2 (95%CI, 2.34-74.2)] and obesity [13.3 (95%CI, 2.38-74.4)], respectively. After adjustment by age in logistic regression models, serum levels of PFOA were associated with 29.4-fold (95%CI, 2.90-299.7) increased risk of MetS. Increased PFOA levels were also correlated with MetS [29.4 (95%CI, 2.9-299.7)], SBP [10.8 (95%CI, 1.31-90.0)], hypertriglyceridemia [16.6 (95%CI, 1.92-147.1)], and obesity [46.7 (95%CI, 4.47-487.7)] with adjustment for age. This study suggests bodily retention of PFASs and its association with MetS. Further clinical and animal studies are warranted to clarify the putative causal relationship.	●	●		●						-	1	B	A

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献ランク①	文献ランク②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
841	ヒト（代謝）	Zeng, X. W.; Qian, Z.; Emo, B.; Vaughn, M.; Bao, J.; Qin, X. D.; Zhu, Y.; Li, J.; Lee, Y. L.; Dong, G. H.	Association of polyfluoroalkyl chemical exposure with serum lipids in children	2015	Sci Total Environ. 2015 Apr 15;512-513:364-370. doi: 10.1016/j.scitotenv.2015.01.042. Epub 2015 Jan 30.	Perfluoroalkyl and polyfluoroalkyl substances (PFASs), as well as polymers of PFASs, have been widely used in commercial applications and have been detected in humans and the environment. Previous epidemiological studies have shown associations between particular PFAS chemicals and serum lipid concentrations in adults, particularly perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA). There exists, however, limited information concerning the effect of PFASs have on serum lipids among children. In the present cross-sectional study, 225 Taiwanese children (12-15 years of age) were recruited to determine the relationship between serum level PFASs and lipid concentration. Results showed that eight out of ten particular PFASs were detected in the serum of >94% of the participants. Serum PFOS and perfluorotetradecanoic acid (PFTA) levels were at an order of magnitude higher than the other PFASs, with arithmetical means of 32.4 and 30.7 ng/ml in boys and 34.2 and 27.4 ng/ml in girls, respectively. However, the variation in serum PFTA concentration was quite large. Following covariate adjustment, linear regression models revealed that PFOS, PFOA, and perfluorononanoic acid (PFNA) were positively associated with total cholesterol (TC), low-density lipoprotein (LDL) and triglycerides (TG), particularly for PFOS and PFTA. Quartile analysis, with the lowest exposure quartile as a reference, yielded associations between serum PFTA and elevations in TC (p=0.002) and LDL (p=0.004). Though not statistically significant, high-density lipoprotein (HDL) appeared to decrease linearly across quartiles for PFOS and PFOA exposure. In conclusion, a significant association was observed between serum PFASs and lipid level in Taiwanese children. These findings for PFTA are novel, and emphasize the need to investigate the exposure route and toxicological evidence of PFASs beyond PFOS and PFOA.	●	●	●				●			-		B	B
842	ヒト（代謝）	Zong, G.; Grandjean, P.; Wang, X.; Sun, Q.	Lactation history, serum concentrations of persistent organic pollutants, and maternal risk of diabetes	2016	Environ Res. 2016 Oct;150:282-288. doi: 10.1016/j.envres.2016.06.023. Epub 2016 Jun 20.	OBJECTIVE: Lactation may help curb diabetes risk and is also known as an excretion route for some environmental pollutants. We evaluated associations of lifetime lactation history with serum concentrations of persistent organic pollutants (POPs) in the National Health and Nutrition Examination Survey 1999-2006, and examined whether potentially diabetogenic POPs account for associations between lactation and diabetes.RESEARCH DESIGN AND METHODS: Among 4479 parous women, breastfeeding history was defined as the number of children breastfed ≥1 month. Diabetes was identified by self-report or hemoglobin A1c >6.5%. Twenty-four POPs were measured in serum among subsamples of 668 to 1073 participants.RESULTS: Compared with women without lactation history, odds ratios (95% confidence intervals) of having diabetes among those with 44563 and ≥3 lactation periods were 0.83(0.61, 1.13) and 0.63(0.44, 0.91; P trend=0.03). Lifetime lactation history was inversely associated with serum concentrations of 17 out of the 24 organochlorine pesticides, polychlorinated biphenyl congeners (PCBs), and perfluoroalkyl substances (Ptrend<0.05). Comparing the ≥3 lactations group with women without a lactation history, the relative reduction of POPs ranged from 0.12 (PCB-196) to 0.3 (oxychlordane). The inverse association between lactation and diabetes was slightly attenuated after adjustment for POPs. Age-stratified analyses showed that the inverse association between lactation periods and serum POP concentrations was observed primarily among participants <60 years, whereas age did not significantly modify the association between lactation history and diabetes prevalence.CONCLUSION: Crudely-classified lifetime lactation history was inversely associated with concurrent serum POP concentrations and diabetes prevalence. Prospective studies are needed to clarify how lactation could complement diabetes prevention through decreasing the POP body burdens.	●	●								-		C	B
843	ヒト（代謝）	Fisher, Mandy; Arbuckle, Tye E; Wade, Mike; Haines, Douglas A	Do perfluoroalkyl substances affect metabolic function and plasma lipids? - Analysis of the 2007–2009, Canadian Health Measures Survey (CHMS) Cycle 1	2013	Environ Res. 2013 Feb;121:95-103. doi: 10.1016/j.envres.2012.11.006. Epub 2012 Dec 22.	BACKGROUND: Perfluorinated compounds (PFCs) are man-made chemicals that are heat stable, non-flammable and able to repel both water and oils. Biomonitoring research shows global distribution in human, animal and aquatic environments of these chemicals. PFCs have been shown to activate the peroxisome proliferator-activated receptors which play a large role in metabolism and the regulation of energy homeostasis. Previous epidemiological research has also suggested a potential role of PFCs on lipid and glucose metabolism. OBJECTIVES: The objectives of this study were to examine the association between the levels of perfluorinated compounds perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), and perfluorohexane sulfonate (PFHxS) in plasma and metabolic function and plasma lipid levels. METHODS: Using cross-sectional data from the Canadian Health Measures Survey (Cycle 1 2007-2009) we examined the association in adults between plasma levels of PFOA, PFOS and PFHxS (n=2700) on cholesterol outcomes, metabolic syndrome and glucose homeostasis using multivariate linear and logistic regression models. RESULTS: We found some evidence of a significant association between perfluoroalkyl substances, notably PFHxS, with total cholesterol (TC), low-density lipoprotein cholesterol (LDL), total cholesterol/high density lipoprotein cholesterol ratio (TC/HDL) and non-HDL cholesterol as well as an elevated odds of high cholesterol. We found some associations with PFOA and PFOS in our unweighted models but these results did not remain significant after weighting for sampling strategy. We found no association with metabolic syndrome, or glucose homeostasis parameters. CONCLUSIONS: This study showed lower levels of PFOA and PFOS and slightly higher levels of PFHxS than other published population studies. Our results did not give significant evidence to support the association with cholesterol outcomes with PFOS and PFOA. However, we did observe several significant associations with the PFHxS and cholesterol outcomes (LDL, TC, NON-HDL, TC/HDL ratio).			●	●	●	●	●			-		B	B
844	ヒト（代謝）	Fu, Yaning; Wang, Tieyu; Fu, Quanliang; Wang, Pei; Lu, Yonglong	Associations between serum concentrations of perfluoroalkyl acids and serum lipid levels in a Chinese population	2014	Ecotoxicol Environ Saf. 2014 Aug;106:246-52. doi: 10.1016/j.ecoenv.2014.04.039. Epub 2014 May 23.	Perfluoroalkyl acids (PFAAs) have been used in a variety of products for many years and have been detected worldwide in human serum. Previous studies have suggested the potential effects of PFAAs on serum lipids. To investigate the associations between serum concentrations of PFAAs and serum lipid levels, 133 participants were randomly selected from the people coming for health check-up in Yuanyang Red Cross Hospital of Henan, China. Linear regression analysis revealed that perfluoro-octanoic acid (PFOA), perfluorononanoic acid (PFNA), and perfluorodecanoic acid (PFDA), with a median concentration of 1.43, 0.37, and 0.19 ng/mL, respectively, were positively associated with total cholesterol (TC). Those in the highest quartile of PFOA exposure had In-TC levels 0.24 mmol/L higher than those in the lowest quartile. For PFNA and PFDA, effect estimates were 0.25 and 0.16 mmol/L, respectively. A positive association between high-density lipoprotein cholesterol (HDLC) and PFDA was found, and there was a 0.18 mmol/L increase of HDLC for the top PFDA quartile compared with the lowest quartile. PFOA and PFNA were positively associated with low-density lipoprotein cholesterol (LDLC). Ln-LDLC levels of people in both top PFOA and PFNA quartiles were 0.33 mmol/L higher than those in the lowest quartiles. Logistic regression analysis indicated that increased PFOA and PFOS quartiles were positively associated with an increased risk of abnormal TC and LDLC when controlling for no confounding factors.			●	●			●			-		B	B
845	ヒト（代謝）	Lin, Chien-Yu; Wen, Li Li; Lin, Lian-Yu; Wen, Ting-Wen; Lien, Guang-Wen; Chen, Chia-Yang; Hsu, Sandy H J; Chien, Kuo-Liong; Sung, Fung-Chang; Chen, Pau-Chung; Su, Ta-Chen	Associations between levels of serum perfluorinated chemicals and adiponectin in a young hypertension cohort in Taiwan	2011	Environ Sci Technol. 2011 Dec 15;45(24):10691-8. doi: 10.1021/es201964x. Epub 2011 Nov 17.	In animals, perfluorinated chemicals (PFCs), specifically perfluorooctanoic acid (PFOA) and perfluorooctane sulfate (PFOS), function as peroxisome proliferator-activated receptor (PPAR) alpha agonists. However, the relevance of animal (primarily rodent) data to humans is unresolved. While plasma adiponectin level is very responsive to PPAR gamma agonist drugs, it has not been determined whether adiponectin level is related to serum PFCs concentrations. In the present study, 287 subjects (12-30 years of age) were recruited to determine the relationship between serum level of PFCs and serum level of adiponectin. The results showed males had higher serum PFOS concentrations than females and that those with metabolic syndrome had lower serum PFOA than controls. Besides, it showed regional elevations of the perfluoroundecanoic acid (PFUA) (median concentration: 7.11 ng/mL) in the study subjects. No relationship of PFOA, PFOS, PFUA, and the sum of all four PFCs was found to glucose homeostasis, adiponectin level, lipid profile, and inflammatory markers. The median and the range of perfluorononanoic acid (PFNA) concentration (in ng/mL; for four categories corresponding to the <50, 50-74, 75-89, and ≥90th percentiles) were 0.38 (0.38-1.68), 3.22 (1.73-4.65), 5.85 (4.75-8.29), 10.56 (8.40-25.40), respectively. After controlling for confounding factors, multiple linear regression analysis revealed that the mean natural log-transformed level of adiponectin increased significantly across categories of PFNA (in ng/mL; 8.78, 8.73, 9.06, 9.36; P for trend = 0.010 in the full model). In conclusion, higher serum PFNA concentration is associated with elevated serum adiponectin concentration.			●							-		B	B
846	ヒト（代謝）	Château-Degat, Marie-Ludivine; Pereg, Daria; Dallaire, Renée; Ayotte, Pierre; Dery, Serge; Dewailly, Eric	Effects of perfluorooctanesulfonate exposure on plasma lipid levels in the Inuit population of Nunavik (Northern Quebec)	2010	Environ Res. 2010 Oct;110(7):710-7. doi: 10.1016/j.envres.2010.07.003. Epub 2010 Aug 8.	BACKGROUND: Perfluorooctanesulfonate (PFOS) was used as a surfactant in various commercial products. In rodents, exposure to this compound induced various health effects, including hypolipidemia. In human populations, the potential toxicity of PFOS is not yet fully characterized, but indications of effects on lipids are reported. A recent study reported an increase in plasma cholesterol associated with exposure to perfluorinated compounds in humans exposed through drinking water, but similar effects were not reported in all exposed human populations. PFOS is widely distributed in the environment, including the arctic biota. The Inuit of Nunavik are exposed to environmental contaminants through the consumption of fish and game. This diet is also a source of omega3-polyunsaturated fatty acids (n-3 PUFAs) that are known to lower plasma triacylglycerols. OBJECTIVE: This cross-sectional epidemiologic study aims at assessing the relationship between PFOS exposure and plasma lipids, while taking account of the concomitant hypolipidemic effect exerted by n-3 PUFAs. METHODS: Plasma concentrations of PFOS and lipids were assessed in Nunavik Inuit adults (n=723) in the framework of a large-scale environmental health study. Associations of exposure levels to age, gender and selected wild food consumption associated with n-3 PUFAs intake, as well as the exposure on lipid levels were investigated by multivariate linear modeling. RESULTS: In the Inuit population, PFOS exposure and n-3 PUFAs intake are related to traditional food consumption. Triacylglycerol and ratio of total cholesterol to high density lipoprotein cholesterol (HDL-C) levels were negatively associated with PFOS plasma levels, while HDL-C levels were positively associated, after adjustment for circulating levels of n-3 PUFAs and for the interaction between gender and PFOS plasma levels. Other plasma lipids, such as low density lipoprotein-cholesterol and non-HDL-C were not related to PFOS plasma concentrations. CONCLUSION: The results of this study show a relationship between PFOS and plasma lipid levels in an environmentally exposed human population, and this effect appears distinct from that of n-3 PUFAs.				●	●		●			-		C	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報対象抽出	文献ランク①	文献ランク②
847	ヒト（代謝）	Karnes, Conny; Winquist, Andrea; Steenland, Kyle	Incidence of type II diabetes in a cohort with substantial exposure to perfluorooctanoic acid	2014	Environ Res. 2014 Jan;128:78-83. doi: 10.1016/j.envres.2013.11.003. Epub 2013 Dec 2.	BACKGROUND: Research suggests an increased type II diabetes mortality risk among workers occupationally exposed to PFOA. However, a cross-sectional study of highly exposed Mid-Ohio Valley community residents did not demonstrate an association between PFOA and type II diabetes. OBJECTIVES: We examined the relationship between exposure to PFOA over time and incidence of type II diabetes in a cohort of community residents and workers exposed to high levels of PFOA via contaminated drinking water. METHODS: Community residents and workers were interviewed in 2008-2011 to obtain medical history and other demographic information. Cumulative serum PFOA exposure estimates were calculated based on residence and occupation locations, and a history of plant emissions. We estimated the risk of developing type II diabetes using Cox proportional hazard models, controlling for demographic characteristics and family history. RESULTS: Out of 32,254 survey respondents, there were 4434 cases of self-reported type II diabetes, of which 4129 were validated through medical record review. In analyses based on validated type II diabetes, there was no trend of increased risk with increased cumulative PFOA serum levels (HRs compared to lowest exposure decile: 0.91 (95% CI: 0.76-1.08), 1.18 (95% CI: 0.99-1.40), 0.96 (95% CI: 0.81-1.15), 1.04 (95% CI: 0.87-1.24), 1.11 (95% CI: 0.93-1.32), 1.06 (95% CI: 0.89-1.26), 1.00 (95% CI: 0.85-1.19), 1.03 (95% CI: 0.86-1.23), 1.01 (95% CI: 0.84-1.20)). There was no association between fasting glucose level and cumulative serum levels of PFOA, after excluding diabetics. CONCLUSIONS: We do not find an association between PFOA exposure and incidence of type II diabetes.				●						-		C	B
848	ヒト（代謝）	Steenland, Kyle; Tinker, Sarah; Frisbee, Stephanie; Ducatman, Alan; Vaccarino, Viola	Association of perfluorooctanoic acid and perfluorooctane sulfonate with serum lipids among adults living near a chemical plant	2009	Am J Epidemiol. 2009 Nov 15;170(10):1268-78. doi: 10.1093/aje/kwp279. Epub 2009 Oct 21.	Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) are compounds that do not occur in nature but have been widely used since World War II and persist indefinitely in the environment. They are present in the serum of Americans with median levels of 4 ng/mL and 21 ng/mL, respectively. PFOA has been positively associated with cholesterol in several studies of workers. A cross-sectional study of lipids and PFOA and PFOS was conducted among 46,294 community residents aged 18 years or above, who drank water contaminated with PFOA from a chemical plant in West Virginia. The mean levels of serum PFOA and PFOS in 2005-2006 were 80 ng/mL (median, 27 ng/mL) and 22 ng/mL (median, 20 ng/mL), respectively. All lipid outcomes except high density lipoprotein cholesterol showed significant increasing trends by increasing decile of either compound; high density lipoprotein cholesterol showed no association. The predicted increase in cholesterol from lowest to highest decile for either compound was 11-12 mg/dL. The odds ratios for high cholesterol (>/=240 mg/dL), by increasing quartile of PFOA, were 1.00, 1.21 (95% confidence interval (CI): 1.12, 1.31), 1.33 (95% CI: 1.23, 1.43), and 1.40 (95% CI: 1.29, 1.51) and were similar for PFOS quartiles. Because these data are cross-sectional, causal inference is limited. Nonetheless, the associations between these compounds and lipids raise concerns, given their common presence in the general population.				●	●	●	●			-		B	B
849	ヒト（代謝）	Huang, Haobin; Wang, Qinxue; He, Xiaowei; Wu, Yanhu; Xu, Cheng	Association between polyfluoroalkyl chemical concentrations and leucocyte telomere length in US adults	2019	Sci Total Environ. 2019 Feb 25;653:547-553. doi: 10.1016/j.scitotenv.2018.10.400. Epub 2018 Oct 30.	Exposure to some environmental chemicals is reportedly associated with the leucocyte telomere length (LTL), but the effects of the non-occupational exposure to polyfluoroalkyl chemical (PFCs) on the LTL are not well understood. Using data from 773 participants in the National Health and Nutrition Examination Survey (NHANES) conducted in 1999-2000, we analysed the association between blood PFC concentrations and LTL. Coefficients (betas) and 95% confidence intervals (CIs) for the blood PFC concentrations in association with the LTL were estimated using multivariate linear regression models after adjustment for age, gender, race, body mass index (BMI), poverty income ratio, educational level, white blood cell count, C-reactive protein and other PFCs. The results identified a strong positive association between the blood perfluorooctane sulfonic acid (PFOS) concentration and LTL in adults, and no associations were found between the LTL and other PFCs. In the linear regression models, each increment of one standard deviation (SD) in the base-10-logarithm-transformed PFOS concentration was associated with a 21-bp increase in the LTL in the fully adjusted model (P窶ｯ=窶ｯ0.033). Moreover, serum PFOS was associated with the LTL mainly in females and individuals aged 40-50, as demonstrated by stratified analyses. These results provide epidemiological evidence showing that environment-related levels of serum PFOS are positively associated with the LTL in adults.		●								-		C	A
850	ヒト（代謝）	Kerger, Brent D; Copeland, Teri L; DeCaprio, Anthony P	Tenuous dose–response correlations for common disease states: case study of cholesterol and perfluorooctanoate/sulfonate (PFOA/PFOS) in the C8 Health Project	2011	Drug Chem Toxicol. 2011 Oct;34(4):396-404. doi: 10.3109/01480545.2011.582502. Epub 2011 Jul 19.	Persistent organic chemicals, such as perfluorooctanoic acid (PFOA), perfluorooctanesulfonate (PFOS), dioxins, and polychlorinated biphenyls, pose investigative challenges because they are found in virtually everyone (there is no unexposed control group). To overcome this problem, outcome data in some studies are sorted by chemical dose level and findings in low-end dose groups are compared to sequential higher dose groups. An example is the C8 Health Project that evaluated serum PFOA/PFOS (C8) and total cholesterol among 46,294 West Virginia residents who lived, worked, or went to school for at least 1 year in a C8 contaminated drinking-water district and were over age 18 in 2005-2006. The risk for high total cholesterol (>240 mg/dL) measured via odds ratios (ORs) in logistic regression models showed sequential OR increases with PFOA quartile, in comparison to the lowest quartile (OR = 1.00), that were each significantly elevated (OR = 1.21, 1.33, and 1.40, respectively), but age, sex, and body mass index were stronger correlates. Importantly, the magnitude of cholesterol increase was small (12 mg/dL from lowest to highest exposure deciles) and comparison to similar statistics for the general U.S. population showed the C8 cohort had lower rates of high cholesterol. This suggests that inadvertent selection bias may have affected the lowest exposure quartile (control group), making tenuous the dose-response relationship between PFOA/PFOS and risk of high cholesterol. This case illustrates the substantial difficulties in assigning toxicological importance to statistical comparisons for common disease states that utilize subgroups with low exposures as an effective control group.						●	●			-		C	B
851	ヒト（代謝）	Kaplan AM	Ammonium perfluorooctanoate	2004	US EPA docket AR-226-1867 and AR 226-1868.	No abstract available							●			US EPA docket を検索したが入手不可		D	D
852	ヒト（代謝）	Andersen, Melvin E; Hagenbuch, Bruno; Apte, Udayan; Corton, J Christopher; Fletcher, Tony; Lau, Christopher; Roth, William L; Staels, Bart; Vega, Gloria L; Clewell, Harvey J 3rd; Longnecker, Matthew P	Why is elevation of serum cholesterol associated with exposure to perfluoroalkyl substances (PFAS) in humans? A workshop report on potential mechanisms	2021	Toxicology. 2021 Jul;459:152845. doi: 10.1016/j.tox.2021.152845. Epub 2021 Jul 8.	Serum concentrations of cholesterol are positively correlated with exposure to perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS) in humans. The associated change in cholesterol is small across a broad range of exposure to PFOA and PFOS. Animal studies generally have not indicated a mechanism that would account for the association in humans. The extent to which the relationship is causal is an open question. Nonetheless, the association is of particular importance because increased serum cholesterol has been considered as an endpoint to derive a point of departure in at least one recent risk assessment. To gain insight into potential mechanisms for the association, both causal and non-causal, an expert workshop was held Oct 31 and Nov 1, 2019 to discuss relevant data and propose new studies. In this report, we summarize the relevant background data, the discussion among the attendees, and their recommendations for further research.									●	-		B	B
853	ヒト（代謝）	Batzella, Erich; Girardi, Paolo; Russo, Francesca; Pitter, Gisella; Da Re, Filippo; Fletcher, Tony; Canova, Cristina	Perfluoroalkyl substance mixtures and cardio-metabolic outcomes in highly exposed male workers in the Veneto Region: A mixture-based approach	2022	Environ Res. 2022 Sep;212(Pt A):113225. doi: 10.1016/j.envres.2022.113225. Epub 2022 Apr 4.	BACKGROUND: Perfluoroalkyl substances (PFAS) have been consistently associated with cardio-metabolic traits. Occupational exposures to multiple PFAS with health outcomes have been poorly investigated. The aim of the present study was to examine these associations among former workers involved in PFAS production. METHODS: We considered 232 male ex-employees who had worked in a factory (Trissino, Veneto Region, Italy), which produced PFAS and other chemicals during 1968-2018. Out of twelve serum PFAS, only four (PFOA, PFOS, PFHxS, and PFNA) were quantifiable in at least 50% of samples. Non-fasting serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured. The associations between serum PFAS mixture and considered outcomes were assessed through linear regression mixed models and Weighted Quantile Sum (WQS) regression, adjusting for potential confounders. RESULTS: PFOA was detected at the highest level, with a median concentration (in ng/mL) of 80.8 (min-max: 0.35-13,033), followed by PFOS (median: 8.55, min-max: 0.35-343), PFHxS (median: 6.8, min-max: 0.35-597) and PFNA (median: 0.8, min-max: 0.35-5). We observed that each A quartile increase in the WQS index was positively associated with the levels of TC (β: 8.41, 95% IC: 0.78-16.0), LDL-C (β: 8.02, 95% IC: 1-15.0) and SBP (β: 3.21, 95% IC: 0.82-5.60). No association of serum PFAS concentration on HDL cholesterol and DBP emerged. WQS analyses revealed a major contribution of PFNA and PFHxS for the cholesterol levels, although PFOA reported the highest concentration. PFOA and PFOS emerged as chemicals of concern regarding the association with SBP. CONCLUSIONS: The results showed a clear association between serum PFAS levels and markers of cardiovascular risk and support the importance of clinical surveillance of cardiovascular risk factors in population with a high exposure to PFAS, especially in the occupational setting.									●	-	1	B	A

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献クラン①抽出	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
854	ヒト（代謝）	Canova, Cristina; Di Nisio, Andrea; Barbieri, Giulia; Russo, Francesca; Fletcher, Tony; Batzella, Erich; Dalla Zuanna, Teresa; Pitter, Gisella	PFAS Concentrations and Cardiometabolic Traits in Highly Exposed Children and Adolescents	2021	Int J Environ Res Public Health. 2021 Dec 7;18(24):12881. doi: 10.3390/ijerph182412881.	BACKGROUND: Residents of a large area of north-eastern Italy were exposed for decades to high concentrations of perfluoroalkyl and polyfluoroalkyl substances (PFAS) via drinking water. Despite the large amount of evidence in adults of a positive association between serum PFAS and metabolic outcomes, studies focusing on children and adolescents are limited. We evaluated the associations between serum PFAS concentrations that were quantifiable in at least 40% of samples and lipid profile, blood pressure (BP) and body mass index (BMI) in highly exposed adolescents and children. METHODS: A cross-sectional analysis was conducted in 6669 adolescents (14-19 years) and 2693 children (8-11 years) enrolled in the health surveillance program of the Veneto Region. Non-fasting blood samples were obtained and analyzed for perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), perfluorohexanesulfonic acid (PFHxS), perfluorononanoic acid (PFNA), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and triglycerides. Low-density lipoprotein cholesterol (LDL-C) was calculated. Systolic and diastolic BP were measured, and BMI z-score accounting for age and sex was estimated. The associations between ln-transformed PFAS (and categorized into quartiles) and continuous outcomes were assessed using generalized additive models. The weighted quantile sum regression approach was used to assess PFAS-mixture effects for each outcome. Analyses were stratified by gender and adjusted for potential confounders. RESULTS: Among adolescents, significant associations were detected between all investigated PFAS and TC, LDL-C, and to a lesser extent HDL-C. Among children, PFOS and PFNA had significant associations with TC, LDL-C and HDL-C, while PFOA and PFHxS had significant associations with HDL-C only. Higher serum concentrations of PFAS, particularly PFOS, were associated with lower BMI z-score. No statistically significant associations were observed between PFAS concentrations and BP. These results were confirmed by the multi-pollutant analysis. CONCLUSIONS: Our study supports a consistent association between PFAS concentration and serum lipids, stronger for PFOS and PFNA and with a greater magnitude among children compared to adolescents, and a negative association of PFAS with BMI.									●	-		1	A	A
855	ヒト（代謝）	Zare Jeddi, Maryam; Dalla Zuanna, Teresa; Barbieri, Giulia; Fabricio, Aline S C; Daprà, Francesca; Fletcher, Tony; Russo, Francesca; Pitter, Gisella; Canova, Cristina	Associations of Perfluoroalkyl Substances with Prevalence of Metabolic Syndrome in Highly Exposed Young Adult Community Residents-A Cross-Sectional Study in Veneto Region, Italy	2021	Int J Environ Res Public Health. 2021 Jan 29;18(3):1194. doi: 10.3390/ijerph18031194.	BACKGROUND: Studies on the association between perfluoroalkyl substances (PFAS) and metabolic syndrome (MetS) are limited, and results are inconsistent. We aimed to examine the associations between PFAS serum levels and the prevalence of MetS among highly exposed young adults (ages 20-39) residents of a large area of the Veneto Region (North-Eastern Italy) primarily stemming from PFAS water contamination before September 2013. A total of 15,876 eligible young adult residents living in the investigated municipalities were enrolled in the study from January 2017 to July 2019. METHODS: MetS was defined by using a modified harmonized definition requiring the presence of 3 of the following: obesity (body mass index ≥30), elevated triglyceride (TG), reduced high-density lipoprotein cholesterol, elevated blood pressure, and hemoglobin A1c ≥ 6.1% or self-reported diabetes mellitus or drug treatment for hyperglycemia. Multivariable generalized additive models were performed to identify the associations between four serum PFAS, including perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorohexane sulfonic acid (PFHxS), and perfluorononanoic acid (PFNA), and risk of MetS controlling for potential confounders. RESULTS: A total of 1282 participants (8.1%) met the criteria of MetS with a higher prevalence among men. PFOA, PFHxS, and PFNA were not associated with the risk of MetS, whereas PFOS showed a consistent protective effect against the risk of MetS (OR 0.76, (95% CI: 0.69, 0.85) per ln-PFOS). However, we found statistically significant positive associations between PFAS serum levels and individual components of MetS, mainly elevated blood pressure and elevated TG. CONCLUSION: Our results did not support a consistent association between PFAS and MetS and conflicting findings were observed for individual components of MetS.									●	-			B	B
856	ヒト（心血管系）	Bao, W. W.; Qian, Z. M.; Geiger, S. D.; Liu, E.; Liu, Y.; Wang, S. Q.; Lawrence, W. R.; Yang, B. Y.; Hu, L. W.; Zeng, X. W.; Dong, G. H.	Gender-specific associations between serum isomers of perfluoroalkyl substances and blood pressure among Chinese: Isomers of C8 Health Project in China	2017	Sci Total Environ. 2017 Dec 31;607-608:1304-1312. doi: 10.1016/j.scitotenv.2017.07.124. Epub 2017 Jul 27.	Previous studies have demonstrated associations of perfluoroalkyl substances (PFASs), a group of highly persistent chemicals ubiquitous in wildlife and humans, with hypertension, but the relationships are mixed. Furthermore, academic literature on the relationship between isomers of PFASs and blood pressure (BP) and hypertension in populations from a higher pollution area is scant. We studied 1612 Chinese adults, ages 22-96years old, from Shenyang, China, utilizing high performance liquid chromatography-mass spectrometry to analyze isomers of perfluorooctanesulfonate (PFOS), perfluorooctanoate (PFOA), and other PFASs in blood serum. We used a mercury sphygmomanometer to measure BP. Hypertension was defined as a mean systolic BP (SBP) of at least 140mmHg, and/or diastolic BP (DBP) of at least 90mmHg, and/or use of antihypertensive medications. The results showed that increased serum concentrations of all (both branched and linear) isomers of PFASs were associated with higher prevalence of hypertension. Adjusted odds ratios for hypertension per ln-unit (ng/mL) increase in PFASs ranged from 1.1 (95%CI: 1.04, 1.17) for perfluorobutanoic acid (PFBA) to 1.26 (95%CI: 1.12, 1.42) for 3+4+5m PFOS, and the estimated increases in mean SBP and DBP ranged from 0.80mmHg (95%CI: 0.25, 1.34) for PFBA to 4.51mmHg (95%CI: 3.52, 5.51) for 3+4+5m PFOS, and from 0.51mmHg (95%CI: 0.01, 1.01) for perfluorodecanesulfonate (PFDS) to 2.48 (1.80, 3.16) for perfluorononanoic acid (PFNA), respectively. Compared with linear PFASs isomers, we identified more and stronger associations among branched PFASs isomers and blood pressure. Furthermore, females exhibited consistently stronger effects than males. In conclusion, this study is the first of its kind to show that not only PFASs positively associated with elevated blood pressure, but also that branched PFAS isomers are more frequently associated with blood pressure than linear PFAS isomers.	●	●	●	●						-		B	B
857	ヒト（心血管系）	De Toni, L.; Radu, C. M.; Sabovic, I.; Di Nisio, A.; Dall'Acqua, S.; Guidolin, D.; Spampinato, S.; Campello, E.; Simioni, P.; Foresta, C.	Increased cardiovascular risk associated with chemical sensitivity to perfluoro-octanoic acid: role of impaired platelet aggregation	2020	International Journal of Molecular Sciences. 2020 Jan 8;21(2):399. doi: 10.3390/ijms21020399.	Perfluoro-alkyl substances (PFAS), particularly perfluoro-octanoic acid (PFOA), are persisting environmental chemicals showing bioaccumulation in human tissues. Recently, exposure to PFAS has been associated with increased prevalence of cardiovascular diseases (CVDs). However, a causal role of PFAS in atherosclerosis pathogenesis is under-investigated. Here, we investigated the effect of PFOA exposure on platelets' function, a key player in atherosclerosis process. PFOA accumulation in platelets was evaluated by liquid chromatography-mass spectrometry. Changes in platelets' membrane fluidity and activation after dose-dependent exposure to PFOA were evaluated by merocyanine 540 (MC540) and anti P-Selectin immune staining at flow cytometry, respectively. Intracellular calcium trafficking was analyzed with Fluo4M probe, time-lapse live imaging. Platelets' aggregation state was also evaluated with Multiplate® aggregometry analyzer in 48 male subjects living in a specific area of the Veneto region with high PFAS environmental pollution, and compared with 30 low-exposure control subjects. Platelets' membrane was the major target of PFOA, whose dose-dependent accumulation was associated in turn with increased membrane fluidity, as expected by a computational model; increased activation at resting condition; and both calcium uptake and aggregation upon activation. Finally, exposed subjects had higher serum and platelets levels of PFOA, together with increased aggregation parameters at Multiplate®, compared with controls. These data help to explain the emerging association between PFAS exposure and CVD.	●	●								-		B	B
858	ヒト（心血管系）	Geiger, SD; Xiao, J; Shankar, A.	Positive association between perfluoroalkyl chemicals and hyperuricemia in children	2013	Am J Epidemiol. 2013 Jun 1;177(11):1255-62. doi: 10.1093/aje/kws392. Epub 2013 Apr 3.	Hyperuricemia in children is associated with increased risk of high blood pressure, metabolic syndrome, and future cardiovascular disease. Serum perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) levels have been shown to be positively associated with hyperuricemia in adults, but the association in children remains unexplored. We therefore examined the association between serum PFOA and PFOS levels and hyperuricemia in a representative sample of US children. A cross-sectional study was performed on 1,772 participants ≤18 years of age from the National Health and Nutrition Examination Survey 1999-2000 and 2003-2008. The main outcome of interest was hyperuricemia, defined as serum uric acid levels ≥6 mg/dL. We found that serum levels of PFOA and PFOS were positively associated with hyperuricemia, independent of age, sex, race/ethnicity, body mass index, annual household income, physical activity, serum total cholesterol, and serum cotinine levels. Compared with subjects in quartile 1 (referent), subjects in quartile 4 had multivariable-adjusted odds ratios for hyperuricemia of 1.62 (95% confidence interval: 1.10, 2.37) for PFOA and 1.65 (95% confidence interval: 1.10, 2.49) for PFOS. Our findings indicate that serum perfluoroalkyl chemical levels are significantly associated with hyperuricemia in children even at the lower "background" exposure levels of the US general population.	●	●		●						-		A	B
859	ヒト（心血管系）	Honda-Kohmo, K.; Hutcheson, R.; Innes, K. E.; Conway, B. N.	Perfluoroalkyl substances are inversely associated with coronary heart disease in adults with diabetes	2019	J Diabetes Complications. 2019 Jun;33(6):407-412. doi: 10.1016/j.jdiacomp.2019.02.004. Epub 2019 Feb 20.	AIMS: Perfluoroalkyl substances (PFAS) are environmentally and biologically persistent synthetic environmental contaminants linked to adverse health outcomes. Though null to modest inverse relationships between PFAS and coronary heart disease (CHD) have been reported, studies regarding relationships in high risk populations such as those with diabetes are sparse. We investigated the relationship of PFAS with CHD in persons with diabetes.METHODS: Data on 5270 adults, aged ≥20 years, with diabetes were obtained from the C8 Health Project. Four PFAS were investigated separately: perfluorohexane sulfonate (PFHxS), perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), and perfluorononanoic acid (PFNA).RESULTS: In logistic regression analyses adjusting for age, sex, diabetes duration, BMI, smoking, lipids, WBC, CRP, eGFR, uric acid, hemoglobin and iron, all PFAS were inversely associated with CHD, ORs (95% CIs): PFHxS; 0.72 (0.65-0.79), PFOA; 0.9 (0.81-0.96), PFOS; 0.9 (0.81-0.99), PFNA; 0.88 (0.76-1.02). Stratification by chronic kidney disease status revealed similar inverse relationships for those with and without chronic kidney disease.CONCLUSIONS: In this cross-sectional study of over 5000 adults with diabetes, PFAS showed inverse associations with CHD. These findings may, if confirmed in future studies, provide new physiologic understanding of CHD prevention strategies.	●	●								-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報抽出対象	文献ランク①	文献ランク②
860	ヒト（心血管系）	Huang, M.; Jiao, J.; Zhuang, P.; Chen, X.; Wang, J.; Zhang, Y.	Serum polyfluoroalkyl chemicals are associated with risk of cardiovascular diseases in national US population	2018	Environ Int. 2018 Oct;119:37-46. doi: 10.1016/j.envint.2018.05.051. Epub 2018 Jun 19.	BACKGROUND: Perfluoroalkyl chemicals (PFCs) as possible cardiovascular disrupters are universally detected in humans. However, evidence from epidemiological studies appears insufficient and ambiguous.OBJECTIVES: We aim to examine the serum PFCs levels and their associations with the prevalence of cardiovascular diseases (CVD) and related outcomes in general US population.METHODS: We investigated the serum levels of 12 major PFCs, including perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorohexane sulfonic acid (PFHxS), 2-(N-ethyl-perfluorooctane sulfonamido) acetate (EPAH), 2-(N-methyl-perfluorooctane sulfonamido) acetate (MPAH), perfluorodecanoic acid (PFDE), perfluorobutane sulfonate (PFBS), perfluoroheptanoic acid (PFHP), perfluorononanoic acid (PFNA), perfluorooctane sulfonamide (PFSA), perfluoroundecanoic acid (PFUA), and perfluorododecanoic acid (PFDO), in 10859 participants from the National Health and Nutritional Examination Survey (NHANES) 1999-2014. Logistic regression models were used to estimate the associations between serum PFCs and 5 self-reported CVD outcomes, including congestive heart failure, coronary heart disease, angina pectoris, heart attack, and stroke. Linear regression analyses were used to estimate the PFCs and their associations with 8 traditional CVD risk factors like serum triglyceride and total cholesterol.RESULTS: In multivariable-adjusted models, total PFCs were positively associated with total CVD (p for trend = 0.0166), independent of traditional CVD risk factors, such as smoking status, diabetes, hypertension and serum cholesterol level. Compared with reference quartile of total PFCs levels, the multivariable adjusted odds ratios in increasing quartiles were 1.23 [95% confidence interval (CI): 0.91-1.66], 1.47 (95% CI: 1.14-1.89) and 1.45 (95% CI: 1.06-1.98) for total CVD. Similar positive associations were found if considering individual PFCs including PFOS, PFUA, MPAH, EPAH, PFDO, PFSA and PFBS. In addition, serum levels of MPAH and PFDO were positively associated with congestive heart failure; PFNA, PFDE, and PFUA were positively associated with coronary heart disease; PFUA and PFDO were positively associated with angina pectoris; and PFNA was positively associated with heart attack.CONCLUSIONS: Our findings suggested that exposure to PFCs was positively associated with risk of CVD. Further longitudinal studies are needed to increase our understanding about the role of PFCs exposure in the prevalence of CVD.	●	●	●	●						-	1	A	A
861	ヒト（心血管系）	Leonard, R. C.; Kreckmann, K. H.; Sakr, C. J.; Symons, J. M.	Retrospective cohort mortality study of workers in a polymer production plant including a reference population of regional workers	2008	Ann Epidemiol. 2008 Jan;18(1):15-22. doi: 10.1016/j.annepidem.2007.06.011. Epub 2007 Sep 27.	PURPOSE: Based on previous reports of increased serum lipid levels in workers at a U.S. polymer manufacturing facility, the study objective was to investigate ischemic heart disease (IHD) mortality as well as a broad range of mortality causes for an occupational cohort at the facility.METHODS: The cohort comprised 6027 men and women who had worked at the facility between 1948 and 2002; these years delimit the mortality follow-up period. Standardized mortality ratios (SMR) were estimated to compare observed numbers of deaths to expected numbers derived from mortality rates for 3 reference populations: the U.S. population, the West Virginia state population, and an 8-state regional employee population from the same company.RESULTS: Most SMR estimates based on U.S. and state populations were below 100 Comparison to the employee population also resulted in many SMR estimates at or near a no-effect level. Relative to the regional worker population, a nonsignificant elevation for IHD mortality was observed (SMR = 109, 0.95 confidence interval [CI]: 96, 124). Mortality associated with diabetes was significantly increased compared to the regional worker population (SMR = 197, 0.95 CI: 123, 298). A corresponding increase in the SMR for IHD and diabetes mortality was not detected for comparisons with the two general populations.CONCLUSIONS: The results reported herein show little evidence of increased cause-specific mortality risks for workers at the plant. This study demonstrates the utility of comparing occupational cohorts with a similar worker reference population in order to reduce bias associated with the healthy worker effect.	●	●		●		●				-		B	B
862	ヒト（心血管系）	Liao, S.; Yao, W.; Cheang, I.; Tang, X.; Yin, T.; Lu, X.; Zhou, Y.; Zhang, H.; Li, X.	Association between perfluoroalkyl acids and the prevalence of hypertension among US adults	2020	Ecotoxicol Environ Saf. 2020 Jun 15;196:110589. doi: 10.1016/j.ecoenv.2020.110589. Epub 2020 Apr 8.	The nonlinear associations of serum perfluoroalkyl acids (PFAAs) with hypertension and blood pressure have not been addressed. Cross-sectional data from 6967 adults (age ≥ 20 years) from the 2003-2012 National Health and Nutrition Examination Survey (NHANES) were analyzed. Hypertension was defined as an average systolic blood pressure above 140 mmHg, an average diastolic blood pressure above 90 mmHg or self-reported use of prescribed medicine for diagnosed hypertension. After multivariable adjustment, compared with the lowest tertile, the odds ratios (ORs) with 0.95 confidence intervals (CIs) of hypertension for the highest tertile of perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorohexane sulfonic acid (PFHxS) and perfluorononanoic acid (PFNA) were 1.32 (1.13, 1.54), 1.14 (0.97, 1.34), 1.16 (0.99, 1.36) and 1.18 (1.01, 1.37), respectively. PFOA and PFNA displayed a J-shaped relationship with the prevalence of hypertension. Furthermore, threshold effect analysis showed that the inflection point of PFOA was 1.80 ng/ml. Each 10-fold change in PFOA exhibited a 0.44 decrease (OR 0.56, 95%CI (0.32, 0.99)) in the odds of hypertension on the left side of the inflection point, and an 0.85 increase (OR 1.85, 95%CI (1.34, 2.54)) on the right side of the inflection point. Threshold effect analysis also indicated that the inflection point of PFNA was 0.53 ng/ml. Each 10-fold change in PFNA exhibited a 0.6 decrease (OR 0.40, 95%CI (0.18, 0.85)) in the odds of hypertension on the left side of the inflection point, and an 0.85 increase (OR 1.64, 95%CI (1.25, 2.14)) on the right side of the inflection point. These cross-sectional data showed a J-shaped association between perfluoroalkyl acids and hypertension.	●	●								-	1	A	B
863	ヒト（心血管系）	Lin, C. Y.; Chen, P. C.; Lo, S. C.; Torng, P. L.; Sung, F. C.; Su, T. C.	The association of carotid intima-media thickness with serum Level of perfluorinated chemicals and endothelium-platelet microparticles in adolescents and young adults	2016	Environ Int. 2016 Sep;94:292-299. doi: 10.1016/j.envint.2016.06.004. Epub 2016 Jun 9.	Perfluorinated chemicals (PFCs) have been widely used in a variety of products worldwide. Our previous study has documented a close association of higher serum level of perfluorooctane sulfonate (PFOS) with an increased carotid intima-media thickness (CIMT) in a cohort of adolescents and young adults. Herein, we further investigated the association of oxidative stress, circulating endothelial microparticles (EMPs) and platelet microparticles (PMPs) with PFCs and CIMT in humans. We recruited 848 subjects (12-30years old) from a population-based sample to determine the relationship between serum levels of PFCs, EMPs (CD62E and CD31+/CD42a-), PMPs (CD62P and CD31+/CD42a+), and the urine levels of 8-hydroxydeoxyguanosine (8-OHdG) and CIMT. The results showed that CD31+/CD42a- (endothelial apoptosis marker) and CD31+/CD42a+ (platelet apoptosis marker) increased significantly across quartiles of PFOS in multiple linear regression analysis. Furthermore, the elevation of CD31+/CD42a- and CD31+/CD42a+ corresponded to the increase of the odds ratios of thicker CIMT (greater than 50th percentile) with higher serum PFOS concentration (greater than 50%) (OR=2.86, 0.95 C.I.=1.69-4.84, P<0.001) in logistic regression models. There was no association between PFC concentration and 8-OHdG. In conclusion, we found the positive association between PFOS and CIMT that was more evident when serum levels of EMPs (CD31+/CD42a-) and PMPs (CD31+/CD42a+) were elevated. Further studies are warranted to investigate the causal inference of PFOS exposure on endothelial cell damage and atherosclerosis.	●	●	●							-		B	B
864	ヒト（心血管系）	Lin, P. D.; Cardenas, A.; Hauser, R.; Gold, D. R.; Kleinman, K. P.; Hivert, M. F.; Calafat, A. M.; Webster, T. F.; Horton, E. S.; Oken, E.	Per- and polyfluoroalkyl substances and blood pressure in pre-diabetic adults-cross-sectional and longitudinal analyses of the diabetes prevention program outcomes study	2020	Environ Int. 2020 Apr;137:105573. doi: 10.1016/j.envint.2020.105573. Epub 2020 Feb 20.	The relationship of plasma concentration of per- and polyfluoroalkyl substances (PFAS) with blood pressure (BP) is uncertain. This study examined cross-sectional and prospective associations of PFAS with BP and hypertension. We quantified plasma PFAS concentrations from 957 participants enrolled in the lifestyle and placebo arms of the Diabetes Prevention Program (DPP), a randomized controlled trial with approximately 15 years of follow-up. We used multivariable linear and logistic regressions to test cross-sectional associations of six PFAS, including perfluorooctanesulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorohexane sulfonic acid (PFHxS), N-ethyl-perfluorooctane sulfonamido acetic acid (EtFOSAA), N-methyl-perfluorooctane sulfonamido acetic acid (MeFOSAA), and perfluorononanoic acid (PFNA), with BP and hypertension prevalence, respectively, at baseline. We used generalized linear mixed models to estimate longitudinal associations between baseline PFAS and the rate of BP changes, and Cox-Proportional hazard models to estimate risk of developing hypertension relative to baseline PFAS. Models were adjusted for baseline age, sex, race/ethnicity, treatment arm, educational attainment, income, marital status, smoking habit, alcohol drinking, and diet. We tested for effect modification by the treatment arm and sex, and accounted for multiple comparisons using the False-Discovery Rate (FDR). PFAS concentrations and hypertension prevalence within the study population (65.3% female, 0.577 White, 0.653 aged 40-59 years) were comparable to the general U.S. population. Cross-sectionally, we found small but statistically significant associations of baseline plasma concentrations of PFOA with systolic BP (β per doubling: 1.49 mmHg, 0.95 CI: 0.29, 2.70); and MeFOSAA with hypertension (RR = 1.09 per doubling, 0.95 CI: 1.01, 1.19). Estimates were not statistically significant after FDR adjustment. Longitudinally, we observed null associations in the placebo arm, but some inverse associations of baseline PFOS and MeFOSAA with systolic BP in the lifestyle arm, perhaps due to regression toward the mean. Baseline PFAS concentrations also were not prospectively associated with hypertension risk. Overall, there were modest and mostly null associations of plasma PFAS concentrations with BP and hypertension.	●	●								-		B	B
865	ヒト（心血管系）	Lind, P. M.; Salihovic, S.; van Bavel, B.; Lind, L.	Circulating levels of perfluoroalkyl substances (PFASs) and carotid artery atherosclerosis	2017	Environ Res. 2017 Jan;152:157-164. doi: 10.1016/j.envres.2016.10.002. Epub 2016 Oct 20.	BACKGROUND AND OBJECTIVE: During recent years, some persistent organic pollutants (POPs) have been linked to atherosclerosis. One group of POPs, the poly- and perfluoroalkyl substances (PFASs) have not been investigated with regard to atherosclerotic plaques.METHODS: Carotid artery atherosclerosis was assessed by ultrasound in 1016 subjects aged 70 years in the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study. Eight PFASs were detected in >75% of participants' plasma by ultra-performance liquid chromatography coupled to tandem mass spectrometry (UPLC-MS/MS).RESULTS: No significant linear associations were observed between the PFASs and intima-media thickness (IMT), or the echogenicity in the intima-media complex (IM-GSM, a marker of lipid infiltration in the artery) when men and women were analyzed together. Neither was occurrence of carotid plaques related to PFASs levels. However, highly significant interactions were observed between some PFASs and sex regarding both IM-GSM and plaque prevalence. Perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), and perfluoroundecanoic acid (PFUnDA), were all related to IM-GSM in a positive fashion in women (p=0.002-0.003), while these relationships were negative in men. The levels of PFUnDA were significantly related to carotid plaque in women (OR 1.59, 95%CI 1.03-2.43, p=0.03), but not in men (OR 0.93, 95%CI 0.62-1.42, p=0.75).CONCLUSIONS: In this cross-sectional study, a pronounced gender difference was observed regarding associations between some PFASs, especially the long-chain PFUnDA, and markers of atherosclerosis, with more pronounced relationships found in women. These findings suggest a sex-specific role for PFASs in atherosclerosis.	●	●	●	●						-		C	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①C	文献クラン②B
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
866	ヒト（心血管系）	Ma, S.; Xu, C.; Ma, J.; Wang, Z.; Zhang, Y.; Shu, Y.; Mo, X.	Association between perfluoroalkyl substance concentrations and blood pressure in adolescents	2019	Environ Pollut. 2019 Nov;254(Pt A):112971. doi: 10.1016/j.envpol.2019.112971. Epub 2019 Jul 30.	The effects of exposure to some environmental chemicals on blood pressure have been determined, but the association between non-occupational exposure to perfluoroalkyl substances (PFASs) and blood pressure in adolescents remains unknown. The association between blood pressure and PFAS concentrations was studied by analysing data from 2251 participants filtered from the population enrolled in the National Health and Nutrition Examination Survey (NHANES) from 2003 to 2012 After adjusting for age, sex, race, BMI, cotinine level, dietary intake of calcium, caloric intake, sodium consumption, potassium consumption and sampling year, we estimated the coefficients (betas) and 0.95 confidence intervals (CIs) for the relationship between PFAS concentrations and blood pressure with multiple linear regression models. Potential non-linear relationships were assessed with restricted cubic spline models. Blood levels of perfluorooctane sulfonic acid (PFOS) had a strong positive association with diastolic blood pressure (DBP) in adolescents in the linear model, while the result was not significant in the non-linear model. No significant association was observed between the concentration of any other PFASs and blood pressure. According to the fully adjusted linear regression model (P = 0.041), the mean DBP values in boys in the higher PFOS quintile were 0.027 greater than the mean DBP values of boys in the lowest PFOS quintile. Furthermore, serum PFOS concentrations predominantly affected blood pressure in male adolescents compared with female adolescents. These results provide epidemiological evidence of PFOS-related increases in DBP. Further research is needed to address related issues.	●	●								-		C	B
867	ヒト（心血管系）	Mattsson, K.; Rignell-Hydbom, A.; Holmberg, S.; Thelin, A.; Jönsson, B. A.; Lindh, C. H.; Sehlstedt, A.; Rylander, L.	Levels of perfluoroalkyl substances and risk of coronary heart disease: Findings from a population-based longitudinal study	2015	Environ Res. 2015 Oct;142:148-54. doi: 10.1016/j.envres.2015.06.033. Epub 2015 Jul 3.	BACKGROUND: Cross-sectional studies have shown an association between exposure to perfluoroalkyl substances (PFASs) and coronary heart disease (CHD). These findings need to be evaluated in longitudinal settings.OBJECTIVES: To investigate the risk of CHD in relation to PFAS levels in a longitudinal setting among Swedish rural residents.METHODS: In a population-based prospective cohort of male farmers and rural residents recruited in 1990-1991, all men who received a CHD diagnosis between 1992 and 2009 were identified from national registers (n=253). For each CHD case, one control, matched for age, was chosen randomly from the cohort. For all cases and controls, levels of eight PFASs at baseline were measured in stored blood samples. In addition, for a subsample, PFAS levels were also measured in serum samples collected at a follow-up in 2002-2003.RESULTS: There were no statistically significant associations between levels of seven of the eight PFASs at baseline and risk for developing CHD. There was a significant association between perfluoroheptanoic acid (PFHpA) and CHD (OR=2.72; 0.95 CI: 1.52, 4.84) for the 3rd quartile and (OR=2.45; 0.95 CI: 1.40, 4.29) for the 4th quartile compared to the lowest quartile. Changes in levels of PFCs between baseline and follow-up did not differ systematically between cases and controls.CONCLUSIONS: This longitudinal study does not lend support to the previously reported cross-sectional relationship between PFAS levels and CHD risk. We found a significant association with PFHpA, but this could be a chance finding, considering its chemical resemblance to other PFASs.	●	●	●	●						-		C	B
868	ヒト（心血管系）	Mi, X.; Yang, Y. Q.; Zeeshan, M.; Wang, Z. B.; Zeng, X. Y.; Zhou, Y.; Yang, B. Y.; Hu, L. W.; Yu, H. Y.; Zeng, X. W.; Liu, R. Q.; Dong, G. H.	Serum levels of per- and polyfluoroalkyl substances alternatives and blood pressure by sex status: Isomers of C8 health project in China	2020	Chemosphere. 2020 Dec;261:127691. doi: 10.1016/j.chemosphere.2020.127691. Epub 2020 Jul 19.	Several in vitro and in vivo studies have demonstrated the toxicity of perfluoroalkyl and polyfluoroalkyl substances (PFASs) alternatives, however, relevant epidemiological findings remain to be performed. In addition, the association between PFASs alternatives and blood pressure has not been explored. To address this gap, we quantified serum levels of alternatives and legacy PFAS in 1273 healthy Chinese, aged 34-94 years, from "isomers of C8 health project". Our results showed that an increase of serum PFASs levels was correlated with elevated blood pressure and higher prevalence of hypertension: per natural log unit (ng/mL) increase of 0.251388888888889 chlorinated polyfluorinated ether sulfonic acids (Cl-PFESA) elevated 1.31 (95%CI: 0.13, 2.50) mmHg of diastolic pressure (DBP). Adjusted odds ratios (aORs) for hypertension with per natural log increase of 0.251388888888889 and 0.334722222222222 Cl-PFESA were 2.57 (95%CI: 1.86, 3.56) and 1.18 (95%CI: 1.06, 1.32), respectively. When stratified by sex, the effects of PFASs alternatives on increased blood pressure and hypertension were stronger in women. Meanwhile, the association between 0.251388888888889 Cl-PFESA (aOR = 6.81; 95%CI: 3.54, 13.09) and hypertension was stronger than perfluorooctanoic acid (PFOA) (aOR = 2.32, 95%CI: 1.38, 3.91) in women. In conclusion, our pilot study demonstrates that serum concentrations of PFASs alternatives are positively associated with blood pressure. Moreover, women seem to be more susceptible, and alternatives exhibited stronger effects than legacy PFASs.	●	●								-		C	B
869	ヒト（心血管系）	Mobacke, I.; Lind, L.; Dunder, L.; Salihovic, S.; Lind, P. M.	Circulating levels of perfluoroalkyl substances and left ventricular geometry of the heart in the elderly	2018	Environ Int. 2018 Jun;115:295-300. doi: 10.1016/j.envint.2018.03.033. Epub 2018 Apr 3.	AIMS: Some persistent organic pollutants (POPs) such as hexachlorobenzene (HCB) and some polychlorinated biphenyls (PCBs) have been shown to interfere with myocardial function and geometry. We therefore investigated if also another group of POPs: per- and polyfluoroalkyl substances (PFASs) were associated with alterations in left ventricular geometry.METHODS: 801 subjects aged 70 years were investigated in a cross-sectional study within the scope of the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study. Eight PFASs were detected in >75% of participants´ plasma by ultra-performance liquid chromatograph/tandem mass spectrometry. Left ventricular geometry was determined by echocardiography. Multivariable linear regression was used to investigate the associations between PFASs and left ventricular geometry of the heart after exclusion of subjects with previous myocardial infarction (n = 72).RESULTS: When adjusting for multiple comparisons, none of the eight PFASs evaluated were significantly related to left ventricular mass. However, perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), and perfluoroundecanoic acid (PFUnDA) were related to relative wall thickness (RWT) in a negative fashion (p < 0.0021). Besides being inversely related to RWT, PFNA was also positively related to left ventricular end-diastolic volume (LVEDD) (p < 0.0021). These analyses were adjusted for traditional cardiovascular risk factors.CONCLUSION: In this cross-sectional study, several of the PFASs evaluated, especially PFNA, were related to myocardial geometry: a reduction in relative wall thickness and an increase in left ventricular diameter following adjustment for traditional cardiovascular risk factors, suggesting a role for PFASs in cardiac remodeling.	●	●								-		C	B
870	ヒト（心血管系）	Sakr, C. J.; Symons, J. M.; Kreckmann, K. H.; Leonard, R. C.	Ischaemic heart disease mortality study among workers with occupational exposure to ammonium perfluorooctanoate	2009	Occup Environ Med. 2009 Oct;66(10):699-703. doi: 10.1136/oem.2008.041582. Epub 2009 Jun 23.	OBJECTIVES: Ammonium perfluorooctanoate (APFO) is a biopersistent surfactant used in the manufacture of several types of fluoropolymers. Based on previous findings of increased serum lipid levels associated with exposure to APFO, we evaluated ischaemic heart disease (IHD) mortality in a cohort of occupationally exposed workers.METHODS: Relative risks (RR) were estimated from exposure-response analyses of cumulative exposure measures using proportional hazards regression models.RESULTS: 239 IHD deaths have occurred in the cohort of 4747 workers with work histories from 1948 through 2002 RR estimates indicate no statistically significant increased mortality risk for IHD associated with estimated cumulative exposure. We observed a positive trend only at an exposure lag of 10 years. This finding was not reproduced in other 5-year exposure lags and was attenuated when different cutpoints for exposure categorisation were used.CONCLUSION: This exposure-response study shows no convincing evidence of increased IHD mortality risk for APFO-exposed workers at this plant. Further studies evaluating the incidence of IHD are being conducted.	●	●		●		●				-		C	B
871	ヒト（心血管系）	Schiller, J. S.; Lucas, J. W.; Ward, B. W.; Peregoy, J. A.	Summary health statistics for U.S. adults: National Health Interview Survey, 2010	2012	Vital Health Stat 10. 2012 Jan;(252):1-207.	OBJECTIVES: This report presents health statistics from the 2010 National Health Interview Survey (NHIS) for the civilian noninstitutionalized adult population, classified by sex, age, race and Hispanic origin, education, family income, poverty status, health insurance coverage, marital status, and place and region of residence. Estimates are presented for selected chronic conditions and mental health characteristics, functional limitations, health status, health behaviors, health care access and utilization, and human immunodeficiency virus testing. Percentages and percent distributions are presented in both age-adjusted and unadjusted versions. DATA SOURCE: NHIS is a household, multistage probability sample survey conducted annually by interviewers of the U.S. Census Bureau for the Centers for Disease Control and Prevention's National Center for Health Statistics. In 2010, data were collected on 27,157 adults in the Sample Adult questionnaire. The conditional response rate was 77.3%, and the final response rate was 60.8%. The health information for adults in this report was obtained from one randomly selected adult per family. In very rare instances where the sample adult was not able to respond for himself or herself, a proxy was used. HIGHLIGHTS: In 2010, 61% of adults aged 18 years and over had excellent or very good health. Twelve percent of adults had been told by a doctor or health professional that they had heart disease, 25% had been told on two or more visits that they had hypertension, 9% had been told they had diabetes, and 22% had been told they had some form of arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia. Twenty-one percent of adults were current smokers, and 21% were former smokers. Based on estimates of body mass index, 35% of adults were overweight and 27% were obese.	●	●								-		C	C
872	ヒト（心血管系）	Shah, D.,ivyang	Healthy worker effect phenomenon	2009	Indian J Occup Environ Med. 2009 Aug;13(2):77-9. doi: 10.4103/0019-5278.55123.	The Healthy Worker Effect (HWE) phenomenon has been under debate since some years. Some epidemiologists regard HWE as an ordinary method problem while others consider it a field of science by itself. This article gives definitions of HWE explained with historical background; discusses factors affecting it and suggests methods to minimize problems associated with it.	●	●								-		C	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
873	ヒト（心血管系）	Shankar, Anoop; Xiao, Jie; Ducatman, Alan	Perfluorooctanoic acid and cardiovascular disease in US adults	2012	Arch Intern Med. 2012 Oct 8;172(18):1397-403. doi: 10.1001/archinternmed.2012.3393.	BACKGROUND: Cardiovascular disease (CVD) is a major public health problem. Identifying novel risk factors for CVD, including widely prevalent environmental exposures, is therefore important. Perfluorooctanoic acid (PFOA) is a manmade chemical used in the manufacture of common household consumer products. Biomonitoring surveys have shown that PFOA is detectable in the blood of more than 98% of the US population. Experimental animal studies suggest that an association between PFOA and CVD is plausible. However, this association in humans has not been previously examined. We therefore examined the independent relationship between serum PFOA levels and CVD outcomes in a representative sample of Americans. METHODS: We examined 1216 subjects (51.2% women) from the 1999-2003 National Health and Nutritional Examination Survey. Serum PFOA levels were examined in quartiles. The main outcomes of interest were self-reported CVD, including coronary heart disease and stroke, and objectively measured peripheral arterial disease (PAD), defined as an ankle-brachial blood pressure index of less than 0.9. RESULTS: We found that increasing serum PFOA levels are positively associated with CVD and PAD, independent of confounders such as age, sex, race/ethnicity, smoking status, body mass index, diabetes mellitus, hypertension, and serum cholesterol level. Compared with quartile 1 (reference) of PFOA level, the multivariable odds ratio (95% CI) among subjects in quartile 4 was 2.01 (1.12-3.60; P = .01 for trend) for CVD and 1.78 (1.03-3.08; P = .04 for trend) for PAD. CONCLUSION: Exposure to PFOA is associated with CVD and PAD, independent of traditional cardiovascular risk factors.	●	●		●		●				-	1	B	A
874	ヒト（心血管系）	Mastrantonio, Marina; Bai, Edoardo; Uccelli, Raffaella; Cordiano, Vincenzo; Screpanti, Augusto; Crosignani, Paolo	Drinking water contamination from perfluoroalkyl substances (PFAS): an ecological mortality study in the Veneto Region, Italy	2018	Eur J Public Health. 2018 Feb 1;28(1):180-185. doi: 10.1093/eurpub/ckx066.	BACKGROUND: Perfluoroalkyl substances (PFAS), a heterogeneous group of highly stable man-made chemicals, have been widely used since 1960s and can be detected almost ubiquitously in all environmental matrices. In Italy, on January 2014, drinking water contamination in an area of the Veneto Region was detected mainly due to the drain of fluorinated chemicals by a manufacturing company operating since 1964. METHODS: The present ecological mortality study was aimed at comparing mortality for some causes of death selected on the basis of previous reported associations, during the period 1980-2013, in municipalities with PFAS contaminated and uncontaminated drinking water on the basis of the levels indicated by the Italian National Health Institute (ISS). Sex-specific number, standardized mortality rates and rate ratios (RR) for PFAS contaminated and uncontaminated areas were computed for each cause of death through the ENEA epidemiological database. RESULTS: In both sexes, statistically significant RRs were detected for all causes mortality, diabetes, cerebrovascular diseases, myocardial infarction and Alzheimer's disease. In females, RRs significantly higher than 1.0 were also observed for kidney and breast cancer, and Parkinson's disease. Increased risk, although not statistically significant, was observed for bladder cancer in both sexes, and for testicular cancer, pancreatic cancer and leukemia in males only. CONCLUSIONS: Higher mortality levels for some causes of death, possibly associated with PFAS exposure, were detected in contaminated municipalities in comparison with uncontaminated ones with similar socioeconomic status and smoking habits. These results warrant further individual level analytic studies to delineate casual associations.			●							-		B	B
875	ヒト（心血管系）	Min, Jin-Young; Lee, Kyung-Jong; Park, Jae-Beom; Min, Kyoung-Bok	Perfluorooctanoic acid exposure is associated with elevated homocysteine and hypertension in US adults	2012	Occup Environ Med. 2012 Sep;69(9):658-62. doi: 10.1136/oemed-2011-100288. Epub 2012 May 31.	OBJECTIVE: To investigate the association between serum perfluorooctanoic acid (PFOA) concentration and cardiovascular disease, as measured by homocysteine level and blood pressure in a representative sample of US adults. METHODS: A cross-sectional study of 2934 adults (≥20 years) who participated in the 2003-2004 and 2005-2006 National Health and Nutrition Examination Survey and had detectable levels of PFOA in their serum. The health effects analysed as potentially associated with PFOA exposure included homocysteine level and blood pressure. RESULTS: The geometric mean value (95% CI) of the study participants' serum PFOA concentration was 4.00 μg/l (95% CI 3.86 to 4.13). The homocysteine and systolic blood pressure were shown to increase significantly with an increase in the log-transformed serum PFOA concentration, after adjusting for potential confounding variables. Adjusted ORs comparing participants at the 80th versus the 20th percentiles were 2.62 for hypertension (95% CI 2.09 to 3.14), and a positive association was also evident in models based on quartiles or based on restricted cubic splines. CONCLUSION: These findings suggest that background exposure to PFOA may continue a risk factor for the development of cardiovascular diseases.				●		●				-		B	B
876	ヒト（心血管系）	Simpson, Chris; Winquist, Andrea; Lally, Cathy; Steenland, Kyle	Relation between perfluorooctanoic acid exposure and strokes in a large cohort living near a chemical plant	2013	Environ Res. 2013 Nov;127:22-8. doi: 10.1016/j.envres.2013.10.002. Epub 2013 Nov 4.	BACKGROUND: A community around a chemical plant was exposed to perfluorooctanoic acid (PFOA) for over 50 years, primarily through drinking water. One cohort study of PFOA-exposed workers found a positive trend with stroke mortality. Other, cross-sectional, studies have found positive associations between serum PFOA and risk factors for stroke, including cholesterol, uric acid, and hypertension. OBJECTIVES: We examined the relation between PFOA exposure and incident strokes (including transient ischemic attacks) in community members, including plant workers. METHODS: Participants completed surveys in 2008-2011 regarding medical history, health-related behaviors, and demographics. Cox proportional hazards models were used to compare the hazard of stroke in relation to time-varying estimated cumulative PFOA serum levels, adjusting for confounders. RESULTS: Of 32,254 survey participants with exposure estimates, 1596 self-reported stroke, of whom 919 had their self-report validated by medical records review. After excluding subjects with strokes before age 20 and subjects born before 1920 or with missing covariate data, 825 cases remained. Compared with the lowest quintile of cumulative exposure, subsequent quintiles in the retrospective analysis had hazard ratios of 1.39 [95% confidence interval, 1.11-1.76], 1.36 [1.08-1.71], 1.45 [1.15-1.82], and 1.13 [0.90-1.44]. Tests for trend with linear or log-transformed cumulative dose were not significant (p=0.52 and 0.59, respectively). Neither an analysis with a 5-year lag, nor prospective analyses restricted to 2005-2011 (302 cases) found positive trends (p=0.44, positive trend; p=0.28, negative trend, respectively). CONCLUSIONS: Overall, our data provide only modest evidence of an association between PFOA and stroke incidence.				●						-		C	B
877	ヒト（心血管系）	Winquist, Andrea; Steenland, Kyle	Modeled PFOA exposure and coronary artery disease, hypertension, and high cholesterol in community and worker cohorts	2014	Environ Health Perspect. 2014 Dec;122(12):1299-305. doi: 10.1289/ehp.1307943. Epub 2014 Sep 26.	BACKGROUND: Several previous studies, mostly cross-sectional, have found associations between perfluorooctanoic acid (PFOA) and high cholesterol levels, but studies of hypertension and heart disease have had inconsistent findings. OBJECTIVES: In this study we examined the association between modeled PFOA exposure and incident hypertension, hypercholesterolemia, and coronary artery disease among workers at a Mid-Ohio Valley chemical plant that used PFOA, and residents of the surrounding community. METHODS: Community- and worker-cohort participants completed surveys during 2008-2011 covering demographics, health-related behaviors, and medical history. Cox proportional hazard models, stratified by birth year, modeled the hazard of each outcome (starting at 20 years of age) as a function of retrospective serum PFOA concentration estimates (generated through fate, transport and exposure modeling), controlling for sex, race, education, smoking, alcohol use, body mass index, and diabetes. RESULTS: Among 32,254 participants (28,541 community; 3,713 worker), 12,325 reported hypertension with medication, 9,909 reported hypercholesterolemia with medication, and 3,147 reported coronary artery disease (2,550 validated). Hypercholesterolemia incidence increased with increasing cumulative PFOA exposure (sum of yearly serum concentration estimates), most notably among males 40-60 years of age. Compared with the lowest exposure quintile (< 142 ng/mL-years), hazard ratios for subsequent quintiles (ng/mL-years: 142 to < 234; 234 to < 630; 630 to < 3,579; ≥ 3,579) were 1.24, 1.17, 1.19, and 1.19 overall and 1.38, 1.32, 1.31, and 1.44 among men 40-60 years of age. There was no apparent association between PFOA exposure and hypertension or coronary artery disease incidence. CONCLUSIONS: Higher PFOA exposure was associated with incident hypercholesterolemia with medication, but not with hypertension or coronary artery disease.				●		●	●		●	-		C	B
878	ヒト（心血管系）	Geiger, SD; Xiao, J; Shankar, A.	No association between perfluoroalkyl chemicals and hypertension in children	2014	Integrated Blood Pressure Control. 2014 Jan 13;7:1-7. doi: 10.2147/IBPC.S47660. eCollection 2014.	BACKGROUND: Hypertension is a leading cause of cardiovascular disease worldwide. Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) are perfluoroalkyl chemicals (PFCs) used in the manufacture of common consumer products and detected in the blood of the majority of Americans. Emerging biological data suggest that PFC exposure may have a role in the development of hypertension. However, the association between PFCs and hypertension has not yet been explored in humans. Therefore, we examined this association in a representative sample of US children. METHODS: A cross-sectional study was performed on 1,655 children from the National Health and Nutrition Examination Survey, 1999-2000 and 2003-2008. The main outcome of interest was hypertension, defined as age, height, and sex specific systolic and/or diastolic blood pressure level at the 95th percentile. RESULTS: We found no association between serum levels of PFOA and PFOS and hypertension in either unadjusted or multivariable-adjusted analyses controlling for age, sex, race-ethnicity, body mass index, annual household income, moderate activity, total serum cholesterol, and serum cotinine. Compared with the lowest quartile, the multivariable-adjusted odds ratio (95% confidence interval) of hypertension in the highest quartile of exposure was 0.69 (0.41-1.17) for PFOA and 0.77 (0.37-1.61) for PFOS (all P-trend values >0.30). CONCLUSION: Our findings indicate that exposure to PFOA or PFOS is not significantly associated with hypertension in children at the lower PFC exposure levels typical of the general population.		●		●						-		C	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献クラン①抽出	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
879	ヒト（心血管系）	Nestel, Paul; Clifton, Peter; Colquhoun, David; Noakes, Manny; Mori, Trevor A; Sullivan, David; Thomas, Beth	Indications for omega-3 longchain polyunsaturated fatty acid in the prevention and treatment of cardiovasculard	2015	Heart Lung Circ. 2015 Aug;24(8):769-79. doi: 10.1016/j.hlc.2015.03.020. Epub 2015 Apr 3.	BACKGROUND: The National Heart Foundation of Australia (NHFA) 2008 review on omega-3 long-chain polyunsaturated fatty acids (LCPUFA) made recommendations with respect to supplementation for primary and secondary prevention of cardiovascular disease. Since then, new findings have been published regarding the relationship between omega-3 polyunsaturated fatty acids, including supplementation, and cardiovascular health. METHODS: A literature search was undertaken in PubMed and Medline, for literature published between January 1, 2007 and August 31, 2013. RESULTS AND CONCLUSIONS: A total of eight research questions were developed and, using the National Health and Medical Research Council's evidence assessment framework, conclusions were made in relation to dietary intake of fish and omega-3 LCPUFA for cardiovascular health. In the evidence published since 2007, this summary of evidence concludes that dietary intake of fish was found to be mostly consistent with respect to protection from heart disease and stroke. Higher fish intake was associated with lower incident rates of heart failure in addition to lower sudden cardiac death, stroke and myocardial infarction. In relation to omega-3 LCPUFA supplementation, neither a beneficial nor adverse effect was demonstrated in primary or secondary prevention of coronary heart disease (CHD). Although the evidence continues to be positive for the role of omega-3 LCPUFA in the treatment of hypertriglyceridaemia and a modest positive benefit in heart failure. No further evidence was found to support the consumption of 2g alpha-linolenic acid (ALA)/day over the current Australian guidelines for 1 g/day.						●			-		C	C
880	ヒト（免疫毒性）	Abraham, K.; Mielke, H.; Fromme, H.; Völkel, W.; Menzel, J.; Peiser, M.; Zepp, F.; Willich, S. N.; Weikert, C.	Internal exposure to perfluoroalkyl substances (PFASs) and biological markers in 101 healthy 1-year-old children: associations between levels of perfluorooctanoic acid (PFOA) and vaccine response	2019	Arch Toxicol. 2020 Jun;94(6):2131-2147. doi: 10.1007/s00204-020-02715-4. Epub 2020 Mar 29.	Perfluoroalkyl substances (PFASs) are a complex group of man-made chemicals with high stability and mobility leading to ubiquitous environmental contamination and accumulation in the food chain. In human serum/plasma samples, perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) are the lead compounds. They are immunotoxic in experimental animals, and epidemiological studies provided evidence of a diminished production of vaccine antibodies in young children. However, information on children of the first year of age is missing but relevant, as they have a relatively high exposure if breastfed, and may have a higher susceptibility as their immune system is developing. In a cross-sectional study with 101 healthy 1-year-old children, internal levels of persistent organic pollutants and a broad panel of biological parameters were investigated at the end of the 1990s. Additional analysis of PFASs resulted in plasma levels (mean ± SD) of PFOA and PFOS of 3.8 ± 1.1 and 6.8 ± 3.4 μg/L, respectively, in the 21 formula-fed children, and of 16.8 ± 6.6 and 15.2 ± 6.9 μg/L in the 80 children exclusively breastfed for at least 4 months. The study revealed significant associations between levels of PFOA, but not of PFOS, and adjusted levels of vaccine antibodies against Haemophilus influenza type b (Hib, r = 0.32), tetanus (r = 0.25) and diphtheria (r = 0.23), with no observed adverse effect concentrations (NOAECs) determined by fitting a knee' function of 12.2, 16.9 and 16.2 μg/L, respectively. The effect size (means for PFOA quintiles Q1 vs. Q5) was quantified to be - 86, - 54 and - 53%, respectively. Furthermore, levels of PFOA were inversely associated with the interferon gamma (IFN_{γ}) production of ex-vivo lymphocytes after stimulation with tetanus and diphtheria toxoid, with an effect size of - 64 and - 59% (means Q1 vs. Q5), respectively. The study revealed no influence of PFOA and PFOS on infections during the first year of life and on levels of cholesterol. Our results confirmed the negative associations of PFAS levels and parameters of immune response observed in other epidemiological studies, with high consistency as well as comparable NOAECs and effects sizes for the three vaccine antibodies investigated, but for PFOA only. Due to reduction of background levels of PFASs during the last 20 years, children in Germany nowadays breastfed for a long duration are for the most part not expected to reach PFOA levels at the end of the breastfeeding period above the NOAECs determined.	●	●	●					●	●	-		B	-
881	ヒト（免疫毒性）	Ait Bamai, Y.; Goudarzi, H.; Araki, A.; Okada, E.; Kashino, I.; Miyashita, C.; Kishi, R.	Effect of prenatal exposure to per- and polyfluoroalkyl substances on childhood allergies and common infectious diseases in children up to age 7 years: The Hokkaido study on environment and children's health	2020	Environ Int. 2020 Oct;143:105979. doi: 10.1016/j.envint.2020.105979. Epub 2020 Jul 24.	Per- and polyfluoroalkyl substances (PFAS) are widely used bio-accumulative chemicals in many industrial and household products. Experimental studies reported that exposure to PFAS results in immunotoxicity. We have previously reported that prenatal exposure to PFAS decreased the risk of allergies, while it increased the risk of infectious diseases at ages 2 and 4 years. However, it remains unclear whether the adverse effects of PFAS on allergies and infectious diseases continue until a reliable age of diagnosing allergies. This study aimed at investigating the effects of prenatal exposure to PFAS on the prevalence of allergies and infectious diseases in children up to age 7, from the Hokkaido Study. Among mother-child pairs enrolled in the Hokkaido study and followed up until the age of 7 years, 2689 participants with maternal PFAS, 1st trimester of pregnancy and 7-year-old questionnaire survey data were included in this study. Eleven PFAS in the 3rd-trimester plasma were measured using ultra-performance liquid chromatography coupled to triple quadrupole tandem mass spectrometry. Wheeze, rhino-conjunctivitis, and eczema were defined using the International Study of Asthma and Allergies on Childhood (ISAAC) questionnaire. History childhood infectious diseases diagnosed by a doctor was assessed by a mother-reported questionnaire at child's age 7 The relative risk of childhood allergies was calculated by generalized estimating equation models. The odds ratio of an episode of infectious diseases was calculated by logistic regression analysis, adjusted for potential confounders. The prevalence of various allergies and infectious diseases was: wheeze, 11.9%; rhino-conjunctivitis, 11.3%; eczema, 21.0%; chickenpox, 61.5%; otitis media, 55.7%; pneumonia, 30.6%; and respiratory syncytial virus infection, 16.8%. Prenatal exposure to perfluorooctanoic acid, perfluorodecanoic acid (PFDA), and perfluoroundecanoic acid (PFUnDA) was inversely associated with rhino-conjunctivitis, while that for perfluorooctanoate (PFOA), perfluorooctane sulfonate, PFUnDA, perfluorododecanoic acid (PFDoDA), and perfluorotridecanoic acid was inversely associated with eczema. For infectious diseases, PFDA and PFDoDA were associated with increased risk of pneumonia and PFOA was associated with increased risk of RSV infection among children not having any siblings (only-one-child). Our results corroborate the hypothesis on immunosuppressive and immunomodulating effects of PFAS on allergies and infectious diseases in children. These effects observed previously at 2 and 4 years continued until the age of 7 years. However, additional studies assessing inflammatory biomarkers along with ISAAC questionnaires, doctor-diagnosed allergies, and longer follow-ups are necessary to better assess the effects of exposure to chemicals on human immune outcomes.	●	●						●		-		1	A	-
882	ヒト（免疫毒性）	Ammitzbøll, C.; Börnsen, L.; Petersen, E. R.; Oturai, A. B.; Søndergaard, H. B.; Grandjean, P.; Sellebjerg, F.	Perfluorinated substances, risk factors for multiple sclerosis and cellular immune activation	2019	J Neuroimmunol. 2019 May 15;330:90-95. doi: 10.1016/j.jneuroim.2019.03.002. Epub 2019 Mar 2.	Perfluorinated alkylated substances (PFASs) have immunomodulatory effects but the impact on multiple sclerosis (MS) and cellular immune functions is only sparsely described. In the present study, we found lower concentrations of the long chain PFAS perfluorooctane sulfonic acid (PFOS) in MS than in healthy controls (HC). In HC, we did not detect associations between PFOS concentrations and immune phenotypes. Analyzing the impact of known MS risk factors on cellular immune functions, we found that smoking and Epstein-Barr nuclear antigen 1 antibodies were associated with distinct circulating immune cell changes. In summary, current background PFAS exposure is not an important risk factor for MS.	●	●								-		B	-
883	ヒト（免疫毒性）	Averina, M.; Brox, J.; Huber, S.; Furberg, A. S.; Sørensen, M.	Serum perfluoroalkyl substances (PFAS) and risk of asthma and various allergies in adolescents	2013	Environ Res. 2019 Feb;169:114-121. doi: 10.1016/j.envres.2018.11.005. Epub 2018 Nov 5.	BACKGROUND: Exposure to environmental pollutants may contribute to the development of asthma and other allergies. The aim of this study was to investigate possible associations between asthma and other allergies with exposure to perfluoroalkyl substances (PFASs) in adolescents from the Arctic region of Norway.METHODS: The Tromsø study Fit Futures 1 (TFF1) and 3-year follow-up Fit Futures 2 study (TFF2) included 675 adolescents that completed a questionnaire about health conditions and underwent a clinical examination with blood tests and fractional nitric oxide (FeNO) measurement. Serum concentrations of 18 PFASs were measured by UHPLC-MS/MS method.RESULTS: Total PFASs (ΣPFAS) serum concentration over 4th quartile was positively associated with asthma in the TFF1 (OR 3.35 (95% CI 1.54-7.29), p = 0.002). Total perfluorooctane sulfonate (ΣPFOS), linear PFOS (linPFOS), linear perfluorohexane sulfonate (linPFHxS) concentrations over 4th quartiles were associated with 2 times higher odds of asthma in the TFF1. The positive associations between ΣPFAS, Σ PFOS, linPFOS and asthma remained statistically significant in the TFF2. ΣPFAS and linPFHxS concentrations over 3rd tertiles were associated with positive marker of eosinophilic airways inflammation FeNO> 25 ppb. Concentrations of ΣPFOS and linPFOS over 3rd quartiles were positively associated with self-reported nickel allergy (OR 2.25 (95% CI 1.17-4.35) p = 0.016 and OR 2.53 (95% CI 1.30-4.90) p = 0.006, respectively). Allergic rhinitis, self-reported pollen allergy, food allergy and atopic eczema were not associated with PFASs concentrations.CONCLUSIONS: This study of Norwegian adolescents showed a positive association between several PFASs and asthma, as well as between PFOS and nickel allergy.	●	●	●							-		B	-
884	ヒト（免疫毒性）	Beck, I. H.; Timmermann, C. A. G.; Nielsen, F.; Schoeters, G.; Jøhnk, C.; Kyhl, H. B.; Høst, A.; Jensen, T. K.	Association between prenatal exposure to perfluoroalkyl substances and asthma in 5-year-old children in the Odense Child Cohort	2016	Environ Health. 2019 Nov 15;18(1):97. doi: 10.1186/s12940-019-0541-z.	BACKGROUND: Asthma is the most common non-communicable disease in children. Prenatal exposure to perfluoroalkyl substances (PFASs), a group of persistent environmental chemicals with endocrine disrupting abilities, has been associated with immunomodulation and may contribute to the aetiology of asthma. We investigated the associations between prenatal exposure to five PFASs and asthma in 5-year-old children.METHODS: We studied 981 mother-child pairs within the Odense Child Cohort (OCC), Denmark. We measured perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorohexane sulfonic acid (PFHxS), perfluorononanoic acid (PFNA) and perfluorodecanoic acid (PFDA) in maternal serum donated in early pregnancy. A standardized questionnaire based on the International Study of Asthma and Allergies in Childhood (ISAAC) was used to assess wheeze, self-reported asthma and doctor-diagnosed asthma among children at age 5 years. Associations were examined using logistic regression analyses adjusting for parity, maternal educational level, maternal pre-pregnancy BMI, asthma predisposition and child sex.RESULTS: Among the 5-year-old children 0.186 reported wheeze and 0.071 reported asthma. We found no association between prenatal exposure to PFAS and doctor-diagnosed asthma or wheeze. Prenatal PFAS exposure was associated with self-reported asthma, although only significant for PFNA (OR = 1.84, 0.95 CI 1.03,3.23).CONCLUSION: Our findings support the suggested immunomodulatory effects of PFASs, however, additional studies are warranted. In order to verify our findings, it is important to re-examine the children with postnatal measurements of serum PFAS concentrations and additional clinical diagnostic testing at an older age where an asthma diagnosis is more valid.	●	●								-		B	-
885	ヒト（免疫毒性）	Blain, A.,my; Tiwari, T.,ejpratap, S.,. P.	Chapter 16: Tetanus	2016	Manual for the Surveillance of Vaccine-Preventable Diseases. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Immunization and Respiratory Diseases	No abstract available	●	●								書籍		C	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
886	ヒト（免疫毒性）	Budtz-Jørgensen, E.; Grandjean, P.	Application of benchmark analysis for mixed contaminant exposures: Mutual adjustment of perfluoroalkylate substances associated with immunotoxicity	2018	PLoS One. 2018 Oct 19;13(10):e0205388. doi: 10.1371/journal.pone.0205388. eCollection 2018.	BACKGROUND: Developmental exposure to perfluorinated alkylate substances (PFASs) is associated with deficient IgG antibody responses to childhood vaccines. As this immunotoxicity outcome may represent a critical effect, calculation of benchmark dose (BMD) results would be useful for defining protective limits of exposure. However, exposures to the major PFASs that are associated with this adverse effect are interrelated, and mutually adjusted BMD results would be desirable.METHODS: We carried out BMD calculations on prospective data from two prospective birth cohort studies from the Faroe Islands with a total of 1146 children. Exposure data included serum concentrations of five major PFASs at birth and at age 5 years and, as outcome parameters, the serum concentrations of specific IgG antibodies against tetanus and diphtheria at ages 5 and 7 We calculated the BMDs and their lower confidence bounds (BMDLs) and included mutual adjustment for five major PFASs. BMD and BMDL were expressed in terms of the serum concentration of the PFASs.RESULTS: The BMDLs for the immunotoxicants were of similar magnitude before and after adjustment. As compared to linear dose-response models, the PFASs showed lower results for a piecewise linear model, which also provided a slightly better fit. Weaker associations with the antibody outcomes were observed after adjustments due to the correlation between the PFASs. However, while the adjustments resulted in elevated BMD results and p values, the BMDL values were not materially changed.CONCLUSIONS: Adjustment for co-exposure to a related immunotoxicant increased both the BMD values and their standard errors, though affected the BMDL values only to a negligible extent. Thus, when correlated toxicants appear to affect the same outcome and none of them is known a priori to be solely responsible, all exposures may be considered responsible in BMD calculations. Our BMDL results, both before and after adjustment are generally below current exposure levels and therefore suggest that all five perfluorinated substances should attract regulatory attention, at least until additional evidence shows otherwise.	●	●	●						●	-		B	-
887	ヒト（免疫毒性）	Buser, M. C.; Scinicariello, F.	Perfluoroalkyl substances and food allergies in adolescents	2016	Environ Int. 2016 Mar;88:74-79. doi: 10.1016/j.envint.2015.12.020. Epub 2015 Dec 23.	Perfluoroalkyl and polyfluoroalkyl substances (PFASs) are a class of organic compounds that are persistent in the environment due to their stable carbon-fluorine backbone, which is not susceptible to degradation. Research suggests these chemicals may exert an immunotoxic effect. The aim of this study is to investigate the associations between four PFASs - perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), and perfluorohexane sulfonic acid (PFHxS) - with food sensitization and food allergies in adolescent participants (ages 12-19years) in the National Health and Nutrition Examination Survey (NHANES) 2005-2006 and 2007-2010, respectively. We performed multivariate logistic regression to analyze the association between individual PFASs with food sensitization (defined as having at least 1 food-specific IgE level≥0.35kU/L) in NHANES 2005-2006 and food allergies (self-reported) in NHANES 2007-2010. Serum PFOA, PFOS, and PFHxS were statistically significantly associated with higher odds to have self-reported food allergies in NHANES 2007-2010. When using IgE levels as a marker of food sensitization, we found that serum PFNA was inversely associated with food sensitization (NHANES 2005-2006). In conclusion, we found that serum levels of PFASs were associated with higher odds to have self-reported food allergies. Conversely, adolescents with higher serum PFNA were less likely to be sensitized to food allergens. These results, along with previous studies, warrant further investigation, such as well-designed longitudinal studies.	●	●	●	●						-		B	-
888	ヒト（免疫毒性）	Cellesi, C.; Michelangeli, C.; Rossolini, G. M.; Giovannoni, F.; Rossolini, A.	Immunity to diphtheria, six to 15 years after a basic three-dose immunization schedule	1989	J Biol Stand. 1989 Jan;17(1):29-34. doi: 10.1016/0092-1157(89)90025-5.	The results of a study of the immunity to diphtheria of 283 girls (9-18 years of age) vaccinated at the age of two years with three doses of vaccine, are reported. The rabbit skin test was used to determine the titre of serum diphtheria antitoxin. 0.558 of the subjects were found to be protected (titre greater than or equal to 0.1 IU/ml), 0.389 were only relatively immune (titre greater than or equal to 0.01- less than 0.01 IU/ml), and 0.053 were unprotected (titre less than 0.01 IU/ml). The antitoxin titres showed a tendency to decrease with time. Even so, 44727 years after vaccination, the percentages of protected and partially protected subjects were still high (95%).	●	●								-		C	-
889	ヒト（免疫毒性）	Chen, Q.; Huang, R.; Hua, L.; Guo, Y.; Huang, L.; Zhao, Y.; Wang, X.; Zhang, J.	Prenatal exposure to perfluorooctane sulfonate impairs placental angiogenesis and induces aberrant expression of LncRNA Xist	2018	Environ Health. 2018 Jan 17;17(1):8. doi: 10.1186/s12940-018-0352-7.	BACKGROUND: Perfluoroalkyl and polyfluoroalkyl substances (PFASs) have been reported to suppress immune function. However, previous studies on prenatal exposure to PFASs and allergic disorders in offspring provided inconsistent results. We aimed to examine the association between prenatal exposure to PFASs and childhood atopic dermatitis (AD) in offspring up to 24 months of age.METHODS: A prospective birth cohort study involving 1056 pregnant women was conducted in two hospitals in Shanghai from 2012 to 2015 Prenatal information was collected by an interview with the women and from medical records. Fetal umbilical cord blood was collected at birth. Cord blood plasma PFASs were measured. Children were followed at 6, 12 and 24 months and information on the development of AD was recorded. AD was diagnosed by 2 dermatologists independently based on the questionnaires. Multiple logistic regression was used to compute odds ratio (OR) and corresponding 0.95 confidence interval (CI) for the association between AD and each PFASs, adjusting for potential confounders.RESULTS: A total of 687 children completed a 2-year follow-up visit and had PFASs measurement. AD was diagnosed in 173 -0.252 children during the first 24 months. In female children, a log-unit increase in perfluorooctanoic acid (PFOA) was associated with a 2.1-fold increase in AD risk (AOR 2.07, 0.95 CI 1.13-3.80) after adjusting for potential confounders. The corresponding risk was 2.22 (1.07-4.58) for perfluorononanoic acid (PFNA). The highest PFOA quartile was significantly associated with AD (2.52, 1.12-5.68) compared with the lowest quartile. The highest quartile of PFNA, perfluorodecanoic acid (PFDA) and perfluorohexane sulfonic acid (PFHxS) were associated with AD with AOR (95% CI) being 2.14 (0.97-4.74), 2.14 (1.00-4.57), and 2.3 (1.03-5.15), respectively. Additionally, the second quartile of perfluorododecanoic acid (PFDoA) was associated with a 3.2-fold increase in AD risk (3.24, 1.44-7.27). However, no significant associations were found in male children.CONCLUSIONS: Prenatal exposure to PFOA, PFDA, PFDoA and PFHxS significantly increased the risk of childhood AD in female children during the first 24 months of life. In addition, the associations between AD with prenatal exposure to PFNA were close to statistical significance.	●	●						●		-	1	A	-
890	ヒト（免疫毒性）	Dalsager, L.; Christensen, N.; Husby, S.; Kyhl, H.; Nielsen, F.; Høst, A.; Grandjean, P.; Jensen, T. K.	Association between prenatal exposure to perfluorinated compounds and symptoms of infections at age 1-4years among 359 children in the Odense Child Cohort	2016	Environ Int. 2016 Nov;96:58-64. doi: 10.1016/j.envint.2016.08.026. Epub 2016 Sep 5.	INTRODUCTION: Perfluorinated alkylated substances (PFAS) are persistent industrial chemicals that have resulted in global environmental exposures. Previous epidemiological studies have reported possible effects on the immune system after developmental PFAS exposure, but the possible impact on childhood infectious disease is unclear.OBJECTIVES: To investigate the association between prenatal exposure to PFAS and symptoms of infections at age 1-4years.METHODS: The Odense Child Cohort is an on-going prospective study on children's health, where serum concentrations of perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorohexane sulfonic acid (PFHxS), perfluorodecanoic acid (PFDA) and perfluorononanoic acid (PFNA) were measured in 649 pregnant women before gestational week 16 Of these women, 359 reported on symptoms of infection in their child every two weeks for a one-year period. The association between prenatal exposure to PFAS and the symptoms was estimated using a logistic regression model and a negative binomial regression model. For the latter, the outcome was reported as an incidence rate-ratio (IRR), and all models were adjusted for maternal age, educational level, parity and child age.RESULTS: On average, the children experienced symptoms of infection 0.23 of the time during one year. PFOS exposure in the high tertile compared to the low tertile was associated with a statistically significant increased proportion of days with fever (IRR: 1.65 (95% CI: 1.24, 2.18), P-trend<0.001) and an increased odds of experiencing days with fever above the median (OR: 2.35 (95% CI: 1.31, 4.11). The latter tendency was also apparent for PFOA (OR: 1.97 (95% CI: 1.07, 3.62). Further, higher concentrations of PFOS and PFOA tended to increase the number of episodes of co-occurrence of fever and coughing and fever and nasal discharge during the one-year study period.CONCLUSION: We found a positive association between prenatal exposure to PFOS and PFOA and the prevalence of fever, which may be a sensitive marker of infection. This finding is in agreement with an immunotoxic effect of prenatal exposure to PFAS. The wider implications for childhood infectious disease deserve attention.	●	●	●	●						-		B	-
891	ヒト（免疫毒性）	Dong, G. H.; Tung, K. Y.; Tsai, C. H.; Liu, M. M.; Wang, D.; Liu, W.; Jin, Y. H.; Hsieh, W. S.; Lee, Y. L.; Chen, P. C.	Serum polyfluoroalkyl concentrations, asthma outcomes, and immunological markers in a case-control study of Taiwanese children	2013	Environ Health Perspect. 2013 Apr;121(4):507-13. doi: 10.1289/ehp.1205351. Epub 2013 Jan 8.	BACKGROUND: Perfluorinated compounds (PFCs) are ubiquitous pollutants. Experimental data suggest that they may be associated with adverse health outcomes, including asthma. However, there is little supporting epidemiological evidence.METHODS: A total of 231 asthmatic children and 225 nonasthmatic controls, all from northern Taiwan, were recruited in the Genetic and Biomarkers study for Childhood Asthma. Structure questionnaires were administered by face-to-face interview. Serum concentrations of 11 PFCs and levels of immunological markers were also measured. Associations of PFC quartiles with concentrations of immunological markers and asthma outcomes were estimated using multivariable regression models.RESULTS: Nine PFCs were detectable in most children (≥ 84.4%), of which perfluorooctane sulfonate (PFOS) was the most abundant (median serum concentrations of 33.9 ng/mL in asthmatics and 28.9 ng/mL in controls). Adjusted odds ratios for asthma among those with the highest versus lowest quartile of PFC exposure ranged from 1.81 (95% CI: 1.02, 3.23) for the perfluorododecanoic acid (PFDoA) to 4.05 (95% CI: 2.21, 7.42) for perfluorooctanic acid (PFOA). PFOS, PFOA, and subsets of the other PFCs were positively associated with serum IgE concentrations, absolute eosinophil counts (AEC), eosinophilic cationic protein (ECP) concentrations, and asthma severity scores among asthmatics.CONCLUSIONS: This study suggests an association between PFC exposure and juvenile asthma. Because of widespread exposure to these chemicals, these findings may be of potential public health concern.	●	●	●	●	●				●	-	1	A	-
892	ヒト（免疫毒性）	Galazka, A; Kardymowicz, B	Immunity against diphtheria in adults in Poland	1989	Epidemiol Infect. 1989 Dec;103(3):587-93. doi: 10.1017/s0950268800030983.	The diphtheria immunity status was determined with the passive haemagglutination technique in 503 sera of 10-90-year-old persons from Warsaw and Olsztyn Provinces. Donors of sera were students, teachers, pregnant women, employees of industry and medical service. The immunity was highest (90% of titers 0.1 IU/ml or higher) in persons below 20 years of age and in persons above 60 years of age (55%). Between these two groups, gaps in immunity exist, the proportion of those immune varying from 36-50% in the 20- 60-year-old groups. Since a large pool of susceptible persons creates an epidemic potential it was suggested that the adult type of tetanus-diphtheria toxoid (Td) should be introduced into the routine immunization schedule for high risk groups. These groups might include professional or age groups who are vulnerable to reintroduction of virulent Corynebacterium diphtheriae such as kindergarten and creches personnel, teachers, students, military service personnel and persons travelling to developing countries.	●	●								-		C	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ランク①	文献ランク②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
893	ヒト（免疫毒性）	Gaylord, A.; Trasande, L.; Kannan, K.; Thomas, K. M.; Lee, S.; Liu, M.; Levine, J.	Persistent organic pollutant exposure and celiac disease: A pilot study	2000	Environ Res. 2020 Jul;186:109439. doi: 10.1016/j.envres.2020.109439. Epub 2020 May 11.	Celiac disease affects approximately 0.01 of the population worldwide. Little is known about environmental factors that may modulate risk in genetically susceptible populations. Persistent organic pollutants (POPs) are known endocrine disruptors and, given the interplay between the endocrine and immune systems, are plausible contributors to celiac disease. The current study aims to elucidate the association between POPs and celiac disease. We conducted a single-site pilot study of 88 patients recruited from NYU Langone's Hassenfeld Children's Hospital outpatient clinic, 30 of which were subsequently diagnosed with celiac disease using standard serology and duodenal biopsy examination. Polybrominated diphenyl ether (PBDEs), perfluoroalkyl substances (PFASs), and p,p'-dichlorodiphenyldichloroethylene (DDE) and HLA-DQ genotype category were measured in blood serum and whole blood, respectively. Multivariable logistic regressions were used to obtain odds ratios for celiac disease associated with serum POP concentrations. Controlling for sex, race, age, BMI, and genetic susceptibility score, patients with higher serum DDE concentrations had 2-fold higher odds of celiac disease (95% CI: 1.08, 3.84). After stratifying by sex, we found higher odds of celiac disease in females with serum concentrations of DDE (OR = 13.0, 0.95 CI = 1.54, 110), PFOS (OR = 12.8, 0.95 CI = 1.17, 141), perfluorooctanoic acid (OR = 20.6, 0.95 CI = 1.13, 375) and in males with serum BDE153, a PBDE congener (OR = 2.28, 0.95 CI = 1.01, 5.18). This is the first study to report on celiac disease with POP exposure in children. These findings raise further questions of how environmental chemicals may affect autoimmunity in genetically susceptible individuals.	●	●								-		B	-
894	ヒト（免疫毒性）	Goudarzi, H.; Miyashita, C.; Okada, E.; Kashino, I.; Chen, C. J.; Ito, S.; Araki, A.; Kobayashi, S.; Matsuura, H.; Kishi, R.	Prenatal exposure to perfluoroalkyl acids and prevalence of infectious diseases up to 4 years of age	2017	Environ Int. 2017 Jul;104:132-138. doi: 10.1016/j.envint.2017.01.024. Epub 2017 Apr 7.	Perfluoroalkyl acids (PFAAs) are synthetic chemicals with ability to repel oils and water, and have been widely used in many industrial and household applications such as adhesives and water- and stain-repellent surfaces to nonstick coatings. Animal studies have shown that PFAAs have immunotoxic effects. However, few epidemiological studies have investigated the effects of PFAAs on infectious diseases occurrence. We examined the relationship between prenatal exposure to PFAAs and prevalence of infectious diseases up to 4years of life. A total of 1558 mother-child pairs, who were enrolled in the Hokkaido Study on Environment and Children's Health, were included in this data analysis. Eleven PFAAs were measured in maternal plasma taken at 28-32weeks of gestation using ultra-performance liquid chromatography coupled to triple quadrupole tandem mass spectrometry. Participant characteristics were obtained from medical birth records and self-administered questionnaires during pregnancy and after delivery. Physicians' diagnosis of common infectious diseases including otitis media, pneumonia, respiratory syncytial virus infection, and varicella up to 4years were extracted from the mother-reported questionnaires. The number of children who developed infectious diseases up to 4years of age was as follows: otitis media, 649 (41.4%); pneumonia, 287 (18.4%); respiratory syncytial virus infection, 197 (12.6%); varicella 589 (37.8%). A total of 1046 -0.671 children had at least one of the diseases defined as total infectious diseases. After adjusting for appropriate confounders, PFOS levels in the highest quartile were associated with increased odds ratios (ORs) of total infectious diseases (Q4 vs. Q1 OR: 1.61; 0.95 CI: 1.18, 2.21; p for trend=0.008) in all children. In addition, perfluorohexane sulfonate (PFHxS) was associated with a higher risk of total infectious diseases only among girls (Q4 vs. Q1 OR: 1.55, 0.95 CI: 0.976, 2.45; p for trend=0.045). We found no association between infectious diseases and other examined PFAAs. Our findings suggest that prenatal exposure to PFOS and PFHxS may associated with infectious diseases occurrence in early life. Therefore, prenatal exposure to PFAAs may be immunotoxic for the immune system in offspring.	●	●		●				●		-	1	A	-
895	ヒト（免疫毒性）	Goudarzi, H.; Miyashita, C.; Okada, E.; Kashino, I.; Kobayashi, S.; Chen, C. J.; Ito, S.; Araki, A.; Matsuura, H.; Ito, Y. M.; Kishi, R.	Effects of prenatal exposure to perfluoroalkyl acids on prevalence of allergic diseases among 4-year-old children	2016	Environ Int. 2016 Sep;94:124-132. doi: 10.1016/j.envint.2016.05.020. Epub 2016 May 26.	Perfluoroalkyl acids (PFAAs) are ubiquitous chemicals extremely resistant and widespread throughout the environment, frequently being detected in human blood samples. Animal studies have revealed that exposure to PFAAs results in immunotoxicity. However, the association between PFAAs, especially long-chain PFAAs, and allergies in humans is not well established. We examined whether prenatal exposure to PFAAs is associated with allergic diseases among 4-year-old children in a large-scale prospective birth cohort in Hokkaido, Japan. In total, 1558 mother-child pairs were included in this study and prenatal levels of eleven PFAAs were measured in maternal plasma samples obtained between 28 and 32weeks of pregnancy by using ultra-performance liquid chromatography-tandem mass spectrometry. Participant demographic and characteristic information were obtained from self-administered pre- and postnatal questionnaires and medical birth records. Infant allergies were assessed using the Japanese version of the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three questionnaire, which was administered 4years post-delivery. Symptoms included eczema, wheezing and rhinoconjunctivitis with a prevalence of 19.0%, 18.7%, and 5.4%, respectively. Associations of PFAA quartiles with allergic outcomes were examined using logistic models. Adjusted odds ratios (ORs) in the 4th quartile vs. 1st quartile (Q4 vs. Q1) for total allergic diseases (including at least one allergic outcome) significantly decreased for perfluorododecanoic acid (PFDoDa) (Q4 vs. Q1 OR: 0.621; 0.95 confidence interval (CI): 0.454, 0.847) and perfluorotridecanoic acid (PFTrDA) (Q4 vs. Q1 OR: 0.712; 0.95 CI: 0.524, 0.966) in all children. We obtained similar results when examining the association between PFAAs and eczema. The adjusted OR (Q4 vs. Q1) for wheezing in relation to higher maternal PFHxS levels was 0.728 (95% CI: 0.497, 1.06) in all children. In conclusion, prenatal exposure to long-chain PFAAs, such as PFDoDa and PFTrDA may have an immunosuppressive effect on allergic diseases in 4-year-old children.	●	●	●	●						-		B	-
896	ヒト（免疫毒性）	Grandjean, P.; Budtz-Jørgensen, E.	Immunotoxicity of perfluorinated alkylates: calculation of benchmark doses based on serum concentrations in children	2013	Environ Health. 2013 Apr 19;12(1):35. doi: 10.1186/1476-069X-12-35.	BACKGROUND: Immune suppression may be a critical effect associated with exposure to perfluorinated compounds (PFCs), as indicated by recent data on vaccine antibody responses in children. Therefore, this information may be crucial when deciding on exposure limits. METHODS: Results obtained from follow-up of a Faroese birth cohort were used. Serum-PFC concentrations were measured at age 5 years, and serum antibody concentrations against tetanus and diphtheria toxoids were obtained at ages 7 years. Benchmark dose results were calculated in terms of serum concentrations for 431 children with complete data using linear and logarithmic curves, and sensitivity analyses were included to explore the impact of the low-dose curve shape. RESULTS: Under different linear assumptions regarding dose-dependence of the effects, benchmark dose levels were about 1.3 ng/mL serum for perfluorooctane sulfonic acid and 0.3 ng/mL serum for perfluorooctanoic acid at a benchmark dose response of 5%. These results are below average serum concentrations reported in recent population studies. Even lower results were obtained using logarithmic dose--response curves. Assumption of no effect below the lowest observed dose resulted in higher benchmark dose results, as did a benchmark response of 10%. CONCLUSIONS: The benchmark dose results obtained are in accordance with recent data on toxicity in experimental models. When the results are converted to approximate exposure limits for drinking water, current limits appear to be several hundred fold too high. Current drinking water limits therefore need to be reconsidered.	●	●		●	●	●				-		B	-
897	ヒト（免疫毒性）	Hanvatananukul, P.,.; Prasarakee, C.,.; Sarachai, S.,.; Aurpibul, L.,.; Sintupat, K.,.; Khampan, R.,.; Saheng, J.,.; Sudjaritruk, T.,.	Seroprevalence of antibodies against diphtheria, tetanus, and pertussis among healthy Thai adolescents	2020	Int J Infect Dis. 2020 Jul;96:422-430. doi: 10.1016/j.ijid.2020.04.088. Epub 2020 May 6.	Objective: To determine the seroprevalence of antibodies against of diphtheria, tetanus, and pertussis among Thai adolescents.	●	●								-		C	-
898	ヒト（免疫毒性）	Hotez, P.	America and Europe's new normal: the return of vaccine-preventable diseases	2019	Pediatr Res. 2019 Jun;85(7):912-914. doi: 10.1038/s41390-019-0354-3. Epub 2019 Feb 27.	No abstract available	●	●								アブストなし、要確認？		D	-
899	ヒト（免疫毒性）	Humblet, Olivier; Diaz-Ramirez, Ledif Grisell; Balmes, John R; Pinney, Susan M; Hiatt, Robert A	Perfluoroalkyl chemicals and asthma among children 12-19 years of age: NHANES (1999-2008)	2014	Environ Health Perspect. 2014 Oct;122(10):1129-33. doi: 10.1289/ehp.1306606. Epub 2014 Jun 6.	BACKGROUND: Perfluoroalkyl chemicals (PFCs) are a family of commonly used industrial chemicals whose persistence and ubiquity in human blood samples has led to concern about possible toxicity. Several animal studies and one recent human study have suggested a link between exposure to PFCs and asthma, although few epidemiologic studies have been conducted. OBJECTIVES: We investigated children's PFC serum concentrations and their associations with asthma-related outcomes. METHODS: We evaluated the association between serum concentrations of eight PFCs, including perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorononanoic acid (PFNA), and perfluorohexane sulfonic acid (PFHxS), with self-reported lifetime asthma, recent wheezing, and current asthma using data from participants 12-19 years of age from the 1999-2000 and 2003-2008 National Health and Nutrition Examination Surveys. RESULTS: In multivariable-adjusted models, PFOA was associated with higher odds of ever having received a diagnosis of asthma [odds ratio (OR) = 1.18; 95% CI: 1.01, 1.39 for a doubling in PFOA], whereas for PFOS there were inverse relationships with both asthma and wheezing (OR = 0.88; 95% CI: 0.74, 1.04, and OR = 0.83; 95% CI: 0.67, 1.02, respectively). The associations were attenuated after accounting for sampling weights. No associations were seen between the other PFCs and any outcome. CONCLUSIONS: This cross-sectional study provides some evidence for associations between exposure to PFCs and asthma-related outcomes in children. The evidence is inconsistent, however, and prospective studies are needed.	●	●		●				●		-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①抽出	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
900	ヒト（免疫毒性）	Impinen, A.; Longnecker, M. P.; Nygaard, U. C.; London, S. J.; Ferguson, K. K.; Haug, L. S.; Granum, B.	Maternal levels of perfluoroalkyl substances (PFASs) during pregnancy and childhood allergy and asthma related outcomes and infections in the Norwegian Mother and Child (MoBa) cohort	2019	Environ Int. 2019 Mar;124:462-472. doi: 10.1016/j.envint.2018.12.041. Epub 2019 Jan 23.	INTRODUCTION: Prenatal exposure to perfluoroalkyl substances (PFASs) has been inconsistently associated with asthma and allergic diseases and increased number of infections in early childhood. We examined the association of PFASs measured in pregnancy with childhood asthma, allergies and common infectious diseases in a prospective pregnancy cohort followed to age 7 years.MATERIAL AND METHODS: Six PFASs (out of 19 measured) with at least 0.8 of measurements above the limit of quantification (LOQ) in maternal plasma during pregnancy in two subcohorts of the Norwegian Mother and Child Cohort Study (MoBa) were analyzed in relation to health outcomes: perfluorooctane sulfonic acid (PFOS), acid (PFOA), perfluorohexane sulfonic acid (PFHxS), perfluorononanoic acid (PFNA), perfluoroundecanoic acid (PFUnDA), and perfluoroheptane sulfonic acid (PFHpS). Follow-up questionnaires were completed at 3 years by 1270 women and at 7 years by 972 women among the 1943 with pregnancy questionnaire and PFAS measures. Health outcomes included parent reports of child's symptoms or doctor diagnosed asthma and allergic conditions at age 7 years and parent-reported frequency of various infections at 3 and 7 years of age. Logistic and Poisson regression were used. The FALSE discovery rate was controlled at 5%. Sensitivity analyses on gender were performed.RESULTS: Among the allergy and asthma outcomes, a statistically significant inverse association was seen between PFUnDA concentrations and ever having atopic eczema in girls. PFUnDA also tended to be inversely associated with both wheeze and asthma. For infections from 0 to 3 and 6 to 7 years, 11 significant positive associations were seen between PFASs and airways infections (bronchitis/pneumonia, throat infection, pseudocroup), ear infection and gastric flu/diarrhea; whereas 6 inverse associations were seen for pseudocroup, ear infections and urinary tract infections. The majority of the findings with respect to infectious diseases were found in girls only.DISCUSSION: With the exception of an inverse association between PFUnDA and eczema, and a tendency of a similar association for wheeze and asthma, maternal PFAS levels during pregnancy showed little association with asthma or allergy related outcomes. Findings from the present study suggest immunosuppressive effects of PFASs on airways infections, such as bronchitis/pneumonia and throat infections, as well as diarrhea/gastric flu. Our results indicate a possible role of gender in the PFAS-health outcome associations.	●	●	●					●		-	1	A	-
901	ヒト（免疫毒性）	Impinen, A.; Nygaard, U. C.; Lødrup Carlsen, K. C.; Mowinckel, P.; Carlsen, K. H.; Haug, L. S.; Granum, B.	Prenatal exposure to perfluoralkyl substances (PFASs) associated with respiratory tract infections but not allergy- and asthma-related health outcomes in childhood	2018	Environ Res. 2018 Jan;160:518-523. doi: 10.1016/j.envres.2017.10.012. Epub 2017 Nov 6.	BACKGROUND: Prenatal exposure to perfluoralkyl substances (PFASs) has been reported to be associated with immunosuppression in early childhood, but with contradictory findings related to atopic and lung diseases.AIM: We aimed to determine if prenatal exposure to PFASs is associated with asthma or other allergic diseases or respiratory tract infections in childhood.METHODS: Nineteen PFASs were measured in cord blood available from 641 infants in the Environment and Childhood Asthma (ECA) prospective birth cohort study. The six most abundant PFASs were perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorooctanesulfonamide (PFOSA), perfluorohexane sulfonic acid (PFHxS), perfluorononanoic acid (PFNA), and perfluoroundecanoic acid (PFUnDA). Health outcomes were assessed at two and ten years of age, and included reported obstructive airways disease (wheeze by 10 years; asthma by 2 and 10 years; reduced lung function at birth; allergic rhinitis by 10 years), atopic dermatitis (AD) by 2 and 10 years, allergic sensitization by 10 years, and episodes of common respiratory tract infections (common cold by 2 years, lower respiratory tract infections (LRTI) by 10 years). The associations between exposure and health outcomes were examined using logistic and Poisson regression.RESULTS: The number of reported airways infections were significantly associated with cord blood concentrations of PFAS; common colds by two years with PFUnDA (β = 0.11 (0.08-0.14)) and LRTIs from 0 to 10 years of age with PFOS (β = 0.5 (0.42-0.57)), PFOA (β = 0.28 (0.22-0.35)), PFOSA (β = 0.1 (0.06-0.14)), PFNA (β = 0.09 (0.03-0.14)) and PFUnDA (β = 0.18 (0.13-0.23)) concentrations. Neither reduced lung function at birth, asthma, allergic rhinitis, AD nor allergic sensitization were significantly associated with any of the PFASs.CONCLUSION: Although prenatal exposure to PFASs was not associated with atopic or lung manifestations by 10 years of age, several PFASs were associated with an increased number of respiratory tract infections in the first 10 years of life, suggesting immunosuppressive effects of PFASs.	●	●		●				●		-	1	A	-
902	ヒト（免疫毒性）	Jackson-Browne, M. S.; Eliot, M.; Patti, M.; Spanier, A. J.; Braun, J. M.	PFAS (per- and polyfluoroalkyl substances) and asthma in young children: NHANES 2013-2014	2020	Int J Hyg Environ Health. 2020 Aug;229:113565. doi: 10.1016/j.ijheh.2020.113565. Epub 2020 May 30.	Per- and polyfluoroalkyl substances (PFAS) are a class of persistent chemicals used as industrial surfactants, fire-fighting foams, and textile treatments. Early childhood exposure to perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorononanoic acid (PFNA), and perfluorohexane sulfonic acid (PFHxS) may affect the immune system to increase the risk of allergic and respiratory diseases. However, there are substantial gaps in our knowledge about the relationship between PFAS and immune-mediated outcomes such as asthma in children. Thus, we examined the cross-sectional associations of serum PFOA, PFOS, PFNA, and PFHxS concentrations with childhood asthma. We used data from children aged 44631 years who participated in the National Health and Nutrition Examination Survey (2013-2014). Serum PFAS concentrations were measured in serum using analytical chemistry methods. Asthma was assessed by parent-reported, doctor-diagnosed, asthma using a standardized questionnaire. Controlling for covariates, we estimated odds ratios for asthma per standard deviation increase in ln-transformed serum PFAS concentrations (n = 607). We also examined effect measure modification by child age, sex, and race/ethnicity. PFOA (1.1; 0.95 CI: 0.8, 1.4), PFOS (1.2; 0.95 CI: 0.8, 1.7), PFNA (1.1; 0.95 CI: 0.8, 1.6), and PFHxS (1.1; 0.95 CI: 0.9, 1.6) were weakly associated with an increased odds of asthma. Age modified associations between serum PFOS, but not other serum PFAS concentrations, and odds of asthma (age x PFOS interaction term p-value = 0.03). Sex and race/ethnicity did not modify these associations. We observed some evidence that serum PFAS concentrations are weakly associated with increased asthma prevalence in US children.	●	●								-	1	A	-
903	ヒト（免疫毒性）	Khetsuriani, N; Zakikhany, K; Jabirov, S; Saparova, N; Ursu, P; Wannemuehler, K; Wassilak, S; Efstratiou, A; Martin, R.	Seroepidemiology of diphtheria and tetanus among children and young adults in Tajikistan: nationwide population-based survey, 2010	2013	Vaccine. 2013 Oct 1;31(42):4917-22. doi: 10.1016/j.vaccine.2013.07.015. Epub 2013 Jul 13.	Background: Tajikistan had a major diphtheria outbreak (≈ 10000 cases) in the 1990 s, which was controlled after nationwide immunization campaigns with diphtheria-tetanus toxoid in 1995 and 1996 Since 2000, only 52 diphtheria cases have been reported. However, in coverage surveys conducted in 2000 and 2005, diphtheria-tetanus-pertussis vaccine coverage was lower than administratively reported estimates raising concerns about potential immunity gaps. To further assess population immunity to diphtheria in Tajikistan, diphtheria antibody testing was included in a large-scale nationwide serosurvey for vaccine-preventable diseases conducted in connection with a poliomyelitis outbreak in 2010 In addition, the serosurvey provided an opportunity to assess population immunity to tetanus.	●	●								-		C	-
904	ヒト（免疫毒性）	Kvalem, H. E.; Nygaard, U. C.; Lødrup Carlsen, K. C.; Carlsen, K. H.; Haug, L. S.; Granum, B.	Perfluoroalkyl substances, airways infections, allergy and asthma related health outcomes - Implications of gender, exposure period and study design	2020	Environ Int. 2020 Jan;134:105259. doi: 10.1016/j.envint.2019.105259. Epub 2019 Nov 13.	INTRODUCTION: Exposure to perfluoroalkyl substances (PFASs) has been inconsistently associated with asthma, allergic diseases and airways infections in early childhood. The aim of the study was, therefore, to investigate the effect of childhood exposure to PFASs on asthma and allergy related outcomes and on airways infections before and during puberty using the prospective birth cohort Environment and Childhood Asthma (ECA) Study. Aspects of gender, exposure period and study design (cross-sectional and longitudinal) were also taken into consideration.MATERIAL AND METHODS: Included in the study was 378 participants with PFAS measurements at age 10 years and follow-up data at ages 10 years (cross sectional data) and 16 years (longitudinal data). Eight PFASs with at least 0.7 of measurements above the limit of quantification (LOQ) in the child's serum were included in the present study: perfluoroheptanoate (PFHpA), perfluorooctanoate (PFOA), perfluorononanoate (PFNA), perfluorodecanoate (PFDA), perfluoroundecanoate (PFUnDA), perfluorohexane sulfonate (PFHxS), perfluoroheptane sulfonate (PFHpS) and perfluorooctane sulfonate (PFOS). The PFAS levels were converted into interquartile range (IQR). In addition, perfluorooctane sulfonamide (PFOSA) detected in 0.6 of the samples, was recoded into "not detected /detected". Binomial, multinomial and linear regression were used, followed by Bonferroni adjustment to correct for multiple comparisons. Sensitivity analyses evaluating the effect of extreme PFAS values and gender were performed.RESULTS: In the cross sectional data at 10 years a positive statistically significant association was seen between PFHpA and asthma in girls. In the longitudinal data, PFNA, PFDA and PFUnDA were inversely associated with atopic dermatitis (AD) in girls and with PFHxS in all participants and in boys. Further, PFNA and PFHpS were positively associated with rhinitis in girls and with PFOA in all participants. There seems to be a suggestive pattern of increased risk of allergic sensitisation in all participants and a decreased risk in boys, but due to different results in main and sensitivity analyses these findings should be interpreted with caution. No associations were found between PFASs and lung function. For airways infections and longitudinal data, PFDA was inversely associated with common cold, while positive association was found for PFHpA, PFOA, PFHpS and PFOS and lower respiratory tract infections (LRTI).DISCUSSION AND CONCLUSION: Our results lend further support for an immunosuppressive effect of PFASs on AD and LRTI. Gender seems to be important for some exposure-health associations. No clear pattern in exposure-health associations was observed with regard to exposure period or study design, with the exception of asthma where significant	●	●						●		-		B	-
905	ヒト（免疫毒性）	Looker, C.; Luster, M. I.; Calafat, A. M.; Johnson, V. J.; Burleson, G. R.; Burleson, F. G.; Fletcher, T.	Influenza vaccine response in adults exposed to perfluorooctanoate and perfluorooctanesulfonate	2014	Toxicol Sci. 2014 Mar;138(1):76-88. doi: 10.1093/toxsci/kft269. Epub 2013 Nov 27.	Supported by several epidemiological studies and a large number of animal studies, certain polyfluorinated alkyl acids are believed to be immunotoxic, affecting particularly humoral immunity. Our aim was to investigate the relationship between the antibody response following vaccination with an inactivated trivalent influenza vaccine and circulating levels of perfluorooctanoate (PFOA) and perfluorooctanesulfonate (PFOS). The study population consisted of 411 adults living in the mid-Ohio region of Ohio and West Virginia where public drinking water had been inadvertently contaminated with PFOA. They participated in a larger cross-sectional study in 2005/2006 and were followed up in 2010, by which time serum levels of PFOA had been substantially reduced but were still well above those found in the general population. Hemagglutination inhibition tests were conducted on serum samples collected preinfluenza vaccination and 21 ± 3 days postvaccination in 2010 Serum samples were also analyzed for PFOA and PFOS concentrations (median: 31.5 and 9.2 ng/ml, respectively). Questionnaires were conducted regarding the occurrence and frequency of recent (during the last 12 months) respiratory infections. Our findings indicated that elevated PFOA serum concentrations are associated with reduced antibody titer rise, particularly to A/H3N2 influenza virus, and an increased risk of not attaining the antibody threshold considered to offer long-term protection. Although the direct relationship between weakened antibody response and clinical risk of influenza is not clear, we did not find evidence for an association between self-reported colds or influenza and PFOA levels nor between PFOS serum concentrations and any of the endpoints examined.	●	●	●	●		●		●		-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
906	ヒト（免疫毒性）	Manzano-Salgado, C. B.; Granum, B.; Lopez-Espinosa, M. J.; Ballester, F.; Iñiguez, C.; Gascón, M.; Martínez, D.; Guxens, M.; Basterretxea, M.; Zabaleta, C.; Schettgen, T.; Sunyer, J.; Vrijheid, M.; Casas, M.	Prenatal exposure to perfluoroalkyl substances, immune-related outcomes, and lung function in children from a Spanish birth cohort study	2019	Int J Hyg Environ Health. 2019 Jul;222(6):945-954. doi: 10.1016/j.ijheh.2019.06.005. Epub 2019 Jun 28.	BACKGROUND: Prenatal exposure to perfluoroalkyl substances (PFASs) has been associated with impaired immune and respiratory health during childhood but the evidence is inconsistent and limited for lung function. We studied the association between prenatal PFASs exposure and immune and respiratory health, including lung function, up to age 7 years in the Spanish INMA birth cohort study.METHODS: We assessed four PFASs in maternal plasma samples collected during the 1st trimester of pregnancy (years: 2003-2008): perfluorohexane sulfonate (PFHxS), perfluorooctane sulfonate (PFOS), perfluorooctanoate (PFOA), and perfluorononanoate (PFNA). Mothers reported the occurrence (yes/no) of lower respiratory tract infections, wheezing, asthma, and eczema in the previous 12 months at 1.5 and 4 years of the child (n = 1188) and at 7 years (n = 1071). At ages 4 (n = 503) and 7 (n = 992) years lung function was assessed using spirometry tests.RESULTS: The most abundant PFASs were PFOS and PFOA (geometric means: 5.8 and 2.31 ng/mL, respectively). The relative risk of asthma during childhood per each doubling in PFNA concentration was 0.74 (95 CI%: 0.57, 0.96). The relative risk of eczema during childhood per every doubling in PFOS concentration was 0.86 (95 CI%: 0.75, 0.98). Higher PFOA concentrations were associated with lower forced vital capacity and lower forced expiratory volume in 1 s z-scores at 4 years [β (95 CI %): -0.17 (-0.34, -0.01) and -0.13 (-0.29, 0.03), respectively], but not at 7 years.CONCLUSION: This longitudinal study suggests that different PFASs may affect the developing immune and respiratory systems differently. Prenatal exposure to PFNA and PFOS may be associated with reduced risk of respiratory and immune outcomes, particularly asthma and eczema whereas exposure to PFOA may be associated with reduced lung function in young children. These mixed results need to be replicated in follow-up studies at later ages.	●	●	●							-	1	A	-
907	ヒト（免疫毒性）	McQuillan, GM; Kruszon-Moran, D; Deforest, A; Chu, SY; Wharton, M.	Serologic immunity to diphtheria and tetanus in the United States	2002	Ann Intern Med. 2002 May 7;136(9):660-6. doi: 10.7326/0003-4819-136-9-200205070-00008.	Background: Serologic data on diseases that are preventable by vaccine are useful to evaluate the success of immunization programs and to identify susceptible subgroups. Objective: To provide national estimates of immunity to diphtheria and tetanus by measurement of serum antibody levels. Design: Examination of data from the Third National Health and Nutrition Examination Survey, a representative cross-sectional sample of the U.S. population. Setting: 89 randomly selected locations throughout the United States. Participants: 18 045 persons 6 years of age or older who were examined from 1988 to 1994. Measurements: Serum samples obtained at a single time point were tested for diphtheria and tetanus antitoxin. Results: Overall, 60.5% of Americans 6 years of age or older had fully protective levels of diphtheria antibody (> or =0.10 IU/mL) and 72.3% had protective levels of tetanus antibody (> 0.15 IU/mL). Ninety-one percent of Americans 6 to 11 years of age had protective levels of both diphtheria and tetanus antibody; this proportion decreased to approximately 30% among persons 70 years of age (29.5% for diphtheria and 31.0% for tetanus). Adult Mexican-Americans were slightly less likely to have protective levels of antibody to both toxins. Only 47% of persons 20 years of age or older had levels that were protective against both diseases, and only 63% of adults who were protected against tetanus were also protected against diphtheria. Conclusions: A substantial proportion of adults in the United States do not have antibody levels that are protective against diphtheria and tetanus. In addition, although the recommended vaccine is a combination of tetanus and diphtheria, only 63% of adults with protective antibody to tetanus also had protective antibody to diphtheria.	●	●								-		C	-
908	ヒト（免疫毒性）	Mogensen, U. B.; Grandjean, P.; Heilmann, C.; Nielsen, F.; Weihe, P.; Budtz-Jørgensen, E.	Structural equation modeling of immunotoxicity associated with exposure to perfluorinated alkylates	2015	Environ Health. 2015 Jun 5;14:47. doi: 10.1186/s12940-015-0032-9.	BACKGROUND: Exposure to perfluorinated alkylate substances (PFASs) is associated with immune suppression in animal models, and serum concentrations of specific antibodies against certain childhood vaccines tend to decrease at higher exposures. As such, we investigated the immunotoxic impacts of the three major PFASs in a Faroese birth cohort.METHODS: A total of 464 children contributed blood samples collected at age 7 years. PFAS concentrations and concentrations of antibodies against diphtheria and tetanus were assessed in serum at age 7 years, and results were available from samples collected at age 5 In addition to standard regressions, structural equation models were generated to determine the association between three major PFASs measured at the two points in time and the two antibody concentrations.RESULTS: Concentrations of all three 7-year PFAS concentrations were individually associated with a decrease in concentrations of antibodies, however, it was not possible to attribute causality to any single PFAS concentration. Hence, the three 7-year concentrations were combined and showed that a 2-fold increase in PFAS was associated with a decrease by 0.544 (95% CI: 22.0%, 73.3%) in the antibody concentration. If considering both the age-5 and age-7 concentrations of the three major PFASs, the exposure showed a slightly greater loss.CONCLUSIONS: These analyses strengthen the evidence of human PFAS immunotoxicity at current exposure levels and reflect the usefulness of structural equation models to adjust for imprecision in the exposure variables.	●	●		●	●	●				-		B	-
909	ヒト（免疫毒性）	Mogensen, U. B.; Grandjean, P.; Nielsen, F.; Weihe, P.; Budtz-Jørgensen, E.	Breastfeeding as an Exposure Pathway for Perfluorinated Alkylates	2015	Environ Sci Technol. 2015 Sep 1;49(17):10466-73. doi: 10.1021/acs.est.5b02237. Epub 2015 Aug 20.	Perfluorinated alkylate substances (PFASs) are widely used and have resulted in human exposures worldwide. PFASs occur in breast milk, and the duration of breastfeeding is associated with serum-PFAS concentrations in children. To determine the time-dependent impact of this exposure pathway, we examined the serum concentrations of five major PFASs in a Faroese birth cohort at birth, and at ages 11, 18, and 60 months. Information about the children's breastfeeding history was obtained from the mothers. The trajectory of serum-PFAS concentrations during months with and without breastfeeding was examined by linear mixed models that accounted for the correlations of the PFAS measurements for each child. The models were adjusted for confounders such as body size. The duration of exclusive breastfeeding was associated with increases of most PFAS concentrations by up to 0.3 per month, with lower increases during partial breast-feeding. In contrast to this main pattern, perfluorohexanesulfonate was not affected by breast-feeding. After cessation of breastfeeding, all serum concentrations decreased. This finding supports the evidence of breastfeeding being an important exposure pathway to some PFASs in infants.	●	●		●	●	●				-		C	-
910	ヒト（免疫毒性）	Pilkerton, C. S.; Hobbs, G. R.; Lilly, C.; Knox, S. S.	Rubella immunity and serum perfluoroalkyl substances: Sex and analytic strategy	2018	PLoS One. 2018 Sep 24;13(9):e0203330. doi: 10.1371/journal.pone.0203330. eCollection 2018.	BACKGROUND: Perfluoroalkyl substances (PFASs) have been associated with decreased immunity to childhood tetanus and diphtheria immunizations. If these vaccinations are vulnerable to influence from PFASs, questions arise about associations with other common inoculations.OBJECTIVE: To examine whether serum PFASs were associated with reduced immunity to rubella immunization, and whether interactions with sex or ethnicity warranted analytic stratification. Usually, toxicology analyses are calculated controlling for race and sex. However, sex differences in immune function have been reported and a reduction of immunity to rubella in women could pose risks such miscarriage.METHODS: We analyzed a nationally representative sample of individuals ≥ 12 years from the National Health and Nutrition Examination Survey (NHANES) for years 1999-2000 and 2003-2004 for whom PFAS measures were available. Our analytic strategy was to start with separate analyses for youth and adults controlling for several covariates including ethnicity and sex, as well as the interaction of these terms with PFASs. If there was a main effect of PFASs and an interaction term, we would stratify analyses of effect size. The outcome variable was Rubella IgG titers by quartile of perfluoroalkyl substances.RESULTS: After exclusion for missing data, the analyzed sample contained 581 adult women, 621 adult men, and 1012 youth. There was no significant effect of PFASs on immunity in youths but a significant effect of both PFOA and PFOS in adults, as well as a significant interaction of PFOA x sex and a borderline significant interaction of PFOS x sex. When effect size analyses were stratified by sex, a significant association between rubella titres and PFOA was found in men but not women and PFOS was not significant in either sex.CONCLUSIONS: These results support our earlier studies showing sex specific responses to PFASs and indicate the importance of thinking carefully about analytic strategies in population based toxicology research.	●	●						●		-		B	-
911	ヒト（免疫毒性）	Qin, X. D.; Qian, Z. M.; Dharmage, S. C.; Perret, J.; Geiger, S. D.; Rigdon, S. E.; Howard, S.; Zeng, X. W.; Hu, L. W.; Yang, B. Y.; Zhou, Y.; Li, M.; Xu, S. L.; Bao, W. W.; Zhang, Y. Z.; Yuan, P.; Wang, J.; Zhang, C.; Tian, Y. P.; Nian, M.; Xiao, X.; Chen, W.; Lee, Y. L.; Dong, G. H.	Association of perfluoroalkyl substances exposure with impaired lung function in children	2017	Environ Res. 2017 May;155:15-21. doi: 10.1016/j.envres.2017.01.025. Epub 2017 Feb 4.	Previous studies have demonstrated associations between serum levels of perfluoroalkyl substances (PFASs) and asthma or asthma related-biomarkers. However, no studies have reported a possible relationship between PFASs exposure and lung function among children. The objective of the present study is to test the association between PFASs exposure and lung function in children from a high exposure area by using a cross-sectional case-control study, which included 132 asthmatic children and 168 non-asthmatic controls recruited from 2009 to 2010 in the Genetic and Biomarkers study for Childhood Asthma. Structured questionnaires were administered face-to-face. Lung function was measured by spirometry. Linear regression models were used to examine the influence of PFASs on lung function. The results showed that asthmatics in our study had significantly higher serum PFAS concentrations than healthy controls. Logistic regression models showed a positive association between PFASs and asthma, with adjusted odds ratios (ORs) ranging from 0.99 (95% confidence interval [CI]: 0.80-1.21) to 2.76 (95% CI: 1.82-4.17). Linear regression modeling showed serum PFASs levels were significantly negatively associated with three pulmonary function measurements (forced vital capacity: FVC; forced expiratory volume in 1s: FEV1; forced expiratory flow 25-75%: FEF25-75) among children with asthma, the adjusted coefficients between lung function and PFASs exposure ranged from -0.055 (95%CI: -0.1 to -0.010) for FVC and perfluorooctane sulfonate (PFOS) to -0.223 (95%CI: -0.4 to -0.045) for FEF25-75 and perfluorooctanoic acid (PFOA). PFASs were not, however, significantly associated with pulmonary function among children without asthma. In conclusion, this study suggests that serum PFASs are associated with decreased lung function among children with asthma.	●	●	●	●						-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①抽出	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
912	ヒト（免疫毒性）	Smit, L. A.; Lenters, V.; Høyer, B. B.; Lindh, C. H.; Pedersen, H. S.; Liermontova, I.; Jönsson, B. A.; Piersma, A. H.; Bonde, J. P.; Toft, G.; Vermeulen, R.; Heederik, D.	Prenatal exposure to environmental chemical contaminants and asthma and eczema in school-age children	2015	Allergy. 2015 Jun;70(6):653-60. doi: 10.1111/all.12605. Epub 2015 Mar 22.	BACKGROUND: Emerging evidence suggests that prenatal or early-life exposures to environmental contaminants may contribute to an increased risk of asthma and allergies in children. We aimed to explore associations of prenatal exposures to a large set of environmental chemical contaminants with asthma and eczema in school-age children.METHODS: We studied 1024 mother-child pairs from Greenland and Ukraine from the INUENDO birth cohort. Data were collected by means of an interview-based questionnaire when the children were 44690 years of age. Questions from the ISAAC study were used to define asthma, eczema, and wheeze. We applied principal components analysis (PCA) to sixteen contaminants in maternal serum sampled during pregnancy, including perfluoroalkyl substances (PFASs), metabolites of diethylhexyl (DEHP) and diisononyl (DiNP) phthalates, PCB-153 and p,p'-DDE. Scores of five principal components (PCs) explaining 0.7 of the variance were included in multiple logistic regression models.RESULTS: In a meta-analysis which included both populations, the PC2 score, reflecting exposure to DiNP, was negatively associated with current eczema (OR 0.71, 0.95 CI 0.52-0.96). Other associations were not consistent between the two populations. In Ukrainian children, the PC3 score (DEHP) was positively associated with current wheeze (adjusted OR 1.56, 0.95 CI 1.03-2.37), whereas the PC5 score, dominated by perfluorooctanoic acid (PFOA), was inversely associated with current wheeze (OR 0.64, 0.41-0.99). In Greenlandic children, a negative association of PC4 (organochlorines) with ever eczema (OR 0.78, 0.61-0.99) was found.CONCLUSIONS: We found limited evidence to support a link between prenatal exposure to environmental chemical contaminants and childhood asthma and eczema. This article is protected by copyright. All rights reserved.	●	●		●					-		B	-
913	ヒト（免疫毒性）	Smith, P.,.J.; Humiston, S.,.G.; Marcuse, E.,.K.; Zhao, Z.,.; Dorell, C.,.G.; Howes, C.,.; Hibbs, B.,.	Parental delay or refusal of vaccine doses, childhood vaccination coverage at 24 months of age, and the Health Belief Model	2011	Public Health Rep. 2011 Jul-Aug;126 Suppl 2(Suppl 2):135-46. doi: 10.1177/00333549111260S215.	Objective: We evaluated the association between parents' beliefs about vaccines, their decision to delay or refuse vaccines for their children, and vaccination coverage of children at aged 24 months. Methods: We used data from 11,206 parents of children aged 24-35 months at the time of the 2009 National Immunization Survey interview and determined their vaccination status at aged 24 months. Data included parents' reports of delay and/or refusal of vaccine doses, psychosocial factors suggested by the Health Belief Model, and provider-reported up-to-date vaccination status. Results: In 2009, approximately 60.2% of parents with children aged 24-35 months neither delayed nor refused vaccines, 25.8% only delayed, 8.2% only refused, and 5.8% both delayed and refused vaccines. Compared with parents who neither delayed nor refused vaccines, parents who delayed and refused vaccines were significantly less likely to believe that vaccines are necessary to protect the health of children (70.1% vs. 96.2%), that their child might get a disease if they aren't vaccinated (71.0% vs. 90.0%), and that vaccines are safe (50.4% vs. 84.9%). Children of parents who delayed and refused also had significantly lower vaccination coverage for nine of the 10 recommended childhood vaccines including diphtheria-tetanus-acellular pertussis (65.3% vs. 85.2%), polio (76.9% vs. 93.8%), and measles-mumps-rubella (68.4% vs. 92.5%). After adjusting for sociodemographic differences, we found that parents who were less likely to agree that vaccines are necessary to protect the health of children, to believe that their child might get a disease if they aren't vaccinated, or to believe that vaccines are safe had significantly lower coverage for all 10 childhood vaccines. Conclusions: Parents who delayed and refused vaccine doses were more likely to have vaccine safety concerns and perceive fewer benefits associated with vaccines. Guidelines published by the American Academy of Pediatrics may assist providers in responding to parents who may delay or refuse vaccines.	●	●							-		C	-
914	ヒト（免疫毒性）	Steenland, Kyle; Zhao, Liping; Winquist, Andrea	A cohort incidence study of workers exposed to perfluorooctanoic acid (PFOA)	2015	Occup Environ Med. 2015 May;72(5):373-80. doi: 10.1136/oemed-2014-102364. Epub 2015 Jan 19.	OBJECTIVES: Determine if perfluorooctanoic acid (PFOA) is associated with an incident disease in an occupational cohort. METHODS: We interviewed 3713 workers or their next of kin in 2008-2011, and sought medical records for self-reported disease. These workers were a subset of a previously studied cohort of 32,254 community residents and workers. We estimated historical PFOA serum levels via a job-exposure matrix based on over 2000 serum measurements. Non-occupational exposure from drinking water was also estimated. Lifetime serum cumulative dose (combining occupational and non-occupational exposure) was our exposure metric. We studied 17 disease outcomes with more than 20 validated cases. RESULTS: The median measured serum level was 113 ng/mL in 2005 (n=1881), compared with 4 ng/mL in the US. Ulcerative colitis (10-year lag) showed a significant trend ($p \leq 0.05$) with increasing dose (quartile rate ratios (RRs)=1.00, 3.00, 3.26, 6.57, n=28, p for trend=0.05), similar to earlier findings in the community study. Rheumatoid arthritis (no lag) showed a positive trend in a categorical trend test (RRs=1.00, 2.11, 4.08, 4.45, n=23, p for trend=0.04). Positive non-significant trends were also observed for prostate cancer, non-hepatitis liver disease and male hypothyroidism, which have been implicated in other studies. A significant negative trend was found for bladder cancer and asthma with medication. No marked trends were seen for high cholesterol, which had been seen in the community study. CONCLUSIONS: Ulcerative colitis and rheumatoid arthritis were positively linked to PFOA exposure among workers. Data were limited by small numbers, under-representation of hard-to-trace decedents and few low-exposed referents.	●	●		●			●	●	-		B	-
915	ヒト（免疫毒性）	Steenland, Kyle; Zhao, Liping; Winquist, Andrea; Parks, Christine	Ulcerative Colitis and Perfluorooctanoic Acid (PFOA) in a Highly Exposed Population of Community Residents and Workers in the Mid-Ohio Valley	2013	Environ Health Perspect. 2013 Aug;121(8):900-5. doi: 10.1289/ehp.1206449. Epub 2013 Jun 4.	BACKGROUND: Little is known about environmental determinants of autoimmune diseases. OBJECTIVES: We studied autoimmune diseases in relation to level of exposure to perfluorooctanoic acid (PFOA), which was introduced in the late 1940s and is now ubiquitous in the serum of residents of industrialized countries. METHODS: In 2008-2011 we interviewed 32,254 U.S. adults with high serum PFOA serum levels (median, 28 ng/mL) associated with drinking contaminated water near a chemical plant. Disease history was assessed retrospectively from 1952 or birth (if later than 1952) until interview. Self-reported history of autoimmune disease was validated via medical records. Cumulative exposure to PFOA was derived from estimates of annual mean serum PFOA levels during follow-up, which were based on plant emissions, residential and work history, and a fate-transport model. Cox regression models were used to estimate associations between quartiles of cumulative PFOA serum levels and the incidence of autoimmune diseases with ≥ 50 validated cases, including ulcerative colitis (n = 151), Crohn's disease (n = 96), rheumatoid arthritis (n = 346), insulin-dependent diabetes (presumed to be type 1) (n = 160), lupus (n = 75), and multiple sclerosis (n = 98). RESULTS: The incidence of ulcerative colitis was significantly increased in association with PFOA exposure, with adjusted rate ratios by quartile of exposure of 1.00 (referent), 1.76 (95% CI: 1.04, 2.99), 2.63 (95% CI: 1.56, 4.43), and 2.86 (95% CI: 1.65, 4.96) (ptrend < 0.0001). A prospective analysis of ulcerative colitis diagnosed after the baseline 2005-2006 survey (n = 29 cases) suggested a positive but non-monotonic trend (ptrend = 0.21). DISCUSSION: To our knowledge, this is the first study of associations between this common environmental exposure and autoimmune diseases in humans. We found evidence that PFOA is associated with ulcerative colitis.	●	●		●				●	-		B	-
916	ヒト（免疫毒性）	Stein, C. R.; Ge, Y.; Wolff, M. S.; Ye, X.; Calafat, A. M.; Kraus, T.; Moran, T. M.	Perfluoroalkyl substance serum concentrations and immune response to FluMist vaccination among healthy adults	2016	Environ Res. 2016 Aug;149:171-178. doi: 10.1016/j.envres.2016.05.020. Epub 2016 May 18.	Perfluoroalkyl substances (PFAS) were shown to be immunotoxic in laboratory animals. There is some epidemiological evidence that PFAS exposure is inversely associated with vaccine-induced antibody concentration. We examined immune response to vaccination with FluMist intranasal live attenuated influenza vaccine in relation to four PFAS (perfluorooctanoate, perfluorononanoate, perfluorooctane sulfonate, perfluorohexane sulfonate) serum concentrations among 78 healthy adults vaccinated during the 2010-2011 influenza season. We measured anti-A H1N1 antibody response and cytokine and chemokine concentrations in serum pre-vaccination, 3 days post-vaccination, and 30 days post-vaccination. We measured cytokine, chemokine, and mucosal IgA concentration in nasal secretions 3 days post-vaccination and 30 days post-vaccination. Adults with higher PFAS concentrations were more likely to seroconvert after FluMist vaccination as compared to adults with lower PFAS concentrations. The associations, however, were imprecise and few participants seroconverted as measured either by hemagglutination inhibition -0.09 or immunohistochemical staining (25%). We observed no readily discernable or consistent pattern between PFAS concentration and baseline cytokine, chemokine, or mucosal IgA concentration, or between PFAS concentration and change in these immune markers between baseline and FluMist-response states. The results of this study do not support a reduced immune response to FluMist vaccination among healthy adults in relation to serum PFAS concentration. Given the study's many limitations, however, it does not rule out impaired vaccine response to other vaccines or vaccine components in either children or adults.	●	●	●	●				●	-		B	-
917	ヒト（免疫毒性）	Timmermann, C. A.; Budtz-Jørgensen, E.; Jensen, T. K.; Osuna, C. E.; Petersen, M. S.; Steuerwald, U.; Nielsen, F.; Poulsen, L. K.; Weihe, P.; Grandjean, P.	Association between perfluoroalkyl substance exposure and asthma and allergic disease in children as modified by MMR vaccination	2017	J Immunotoxicol. 2017 Dec;14(1):39-49. doi: 10.1080/1547691X.2016.1254306. Epub 2017 Jan 16.	Perfluoroalkyl substances (PFASs) are highly persistent chemicals that might be associated with asthma and allergy, but the associations remain unclear. Therefore, this study examined whether pre- and postnatal PFAS exposure was associated with childhood asthma and allergy. Measles, mumps, and rubella (MMR) vaccination in early life may have a protective effect against asthma and allergy, and MMR vaccination is therefore taken into account when evaluating these associations. In a cohort of Faroese children whose mothers were recruited during pregnancy, serum concentrations of five PFASs - Perfluorohexane sulfonic acid (PFHxS), perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), and perfluorodecanoic acid (PFDA) - were measured at three timepoints (maternal serum in pregnancy week 34-36 and child serum at ages 5 and 13 years) and their association with immunoglobulin E (IgE) (cord blood and at age 7 years) and asthma/allergic diseases (questionnaires at ages 5 and 13 years and skin prick test at age 13 years) was determined. A total of 559 children were included in the analyses. Interactions with MMR vaccination were evaluated. Among 22 MMR-unvaccinated children, higher levels of the five PFASs at age 5 years were associated with increased odds of asthma at ages 5 and 13. The associations were reversed among MMR-vaccinated children. Prenatal PFAS exposure was not associated with childhood asthma or allergic diseases regardless of MMR vaccination status. In conclusion, PFAS exposure at age 5 was associated with increased risk of asthma among a small subgroup of MMR-unvaccinated children but not among MMR-vaccinated children. While PFAS exposure may impact immune system functions, this study suggests that MMR vaccination might be a potential effect-modifier.	●	●	●						-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
918	ヒト（免疫毒性）	Timmermann, C. A. G.; Jensen, K. J.; Nielsen, F.; Budtz-Jørgensen, E.; van Der Klis, F.; Benn, C. S.; Grandjean, P.; Fisker, A. B.	Serum Perfluoroalkyl Substances, Vaccine Responses, and Morbidity in a Cohort of Guinea-Bissau Children	2020	Environ Health Perspect. 2020 Aug;128(8):87002. doi: 10.1289/EHP6517. Epub 2020 Aug 10.	Perfluoroalkyl substances (PFAS) are a group of widely used persistent chemicals with suspected immunotoxic effects.	●	●						●		-		B	-
919	ヒト（免疫毒性）	Wen, H. J.; Wang, S. L.; Chen, P. C.; Guo, Y. L.	Prenatal perfluorooctanoic acid exposure and glutathione s-transferase T1/M1 genotypes and their association with atopic dermatitis at 2 years of age	2019	PLoS One. 2019 Jan 16;14(1):e0210708. doi: 10.1371/journal.pone.0210708. eCollection 2019.	BACKGROUND: Perfluoroalkyl substance (PFAS) exposure was found associated with atopic diseases. Atopic dermatitis (AD) is a childhood skin disorder. However, the effect of interaction between PFASs and glutathione S-transferase (GST) T1/M1 genotype on AD remains unclear.OBJECTIVE: To investigate the association between gene-environmental interaction and childhood AD using a birth cohort study.METHODS: From 2001 to 2005, 1264 mother-newborn pairs were recruited from eight Taiwanese maternity hospitals. PFAS levels and Genotypes were analysed from cord blood. Information on children's health status including AD occurrence was obtained via phone interviews at 6 months and 2 years. Cord plasma concentrations of nine PFASs were measured via ultra-high performance liquid chromatography/tandem mass spectrometry. GSTT1/M1 was genotyped (null/present) via polymerase chain reaction. Environment-gene interaction effects on AD were assessed using multiple logistic regression analysis.RESULTS: Overall, 839 mother-newborn pairs completed all measurements. The prevalence of ever having physician-diagnosed AD by 2 years of age was 5.4%. Among PFASs, perfluorooctanoic acid (PFOA) was positively associated with AD adjusted for potential confounders. After grouping PFOA levels into three groups: undetected, below and above the median in those with detected, children in above the median group who had the GSTT1-null, or GSTM1-null genotype exhibited a higher odds ratio for AD (OR [95%CI] = 3.45 [1.26-9.99] and 2.92 [1.12-7.91], respectively) as compared to the undetected group.CONCLUSIONS: Our data demonstrated that in-utero PFOA exposure with GSTT1/M1 null genotype were associated with AD. Minimizing early-life PFAS exposure may help against AD development, especially in genetically susceptible individuals.	●	●								-		B	-
920	ヒト（免疫毒性）	Wen, H. J.; Wang, S. L.; Chuang, Y. C.; Chen, P. C.; Guo, Y. L.	Prenatal perfluorooctanoic acid exposure is associated with early onset atopic dermatitis in 5-year-old children	2019	Chemosphere. 2019 Sep;231:25-31. doi: 10.1016/j.chemosphere.2019.05.100. Epub 2019 May 16.	Atopic dermatitis (AD) is the most common childhood skin disease and the first step of atopic march. Perfluoroalkyl substance (PFAS) exposure is associated with atopic diseases, including AD. However, whether PFAS exposure is related to earlier AD onset remains unclear. We aimed to investigate the association between prenatal PFAS exposure and earlier onset of AD in children in a 5-year follow-up study. From 2001 to 2005, 1264 mother-infant pairs were recruited from eight Taiwanese maternity hospitals. PFAS levels were analyzed from cord blood. Information on children's health status, including AD occurrence, was obtained via phone interviews at multiple time points. Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) concentrations were measured by ultra-high performance liquid chromatography/tandem mass spectrometry. Cox proportional hazards models assessed associations between prenatal PFAS exposure and early onset AD. Overall, 863 mother-infant pairs with complete measurements were recruited. The prevalence of physician-diagnosed AD before 5 years of age was 7.1%. PFOA and PFOS concentrations were grouped based on whether they were above the 75th percentile. PFOA exposure was positively associated with earlier onset of AD (Kaplan-Meier estimate, p = 0.014). In the Cox model, after adjusting for sex, family income, parental atopy, breast feeding, and maternal age at childbirth, significance was observed in children above the upper quartile (≥75th) of the PFOA group (hazard ratio: 1.89; 0.95 confidence interval, 1.10-3.16). Our findings suggested that children with higher prenatal PFOA exposure have a higher risk of earlier AD development. Minimizing early life PFAS exposure may help inhibit AD development.	●	●								-	1	A	-
921	ヒト（免疫毒性）	Yusoff, A.,.F.; Mohd Sharani, Z.,.Z.; Kee, C.,.C.; Md Iderus, N.,.H.; , M.,d Zamri, A.,.S.S.; Nagalingam, T.,.; Mohamad Bashaabidin, M.,.S.; Wan Ibadullah, W.,.A.H.; Ghazali, S.,.M.; Yusof, A.,.Y.; Ching, Y.,.M.; Mohamed Nor, N.,.; Kamarudin, B.,.; Ahmad, N.; Arip, M.,.	Seroprevalence of diphtheria toxoid IgG antibodies in the Malaysian population	2021	BMC Infect Dis. 2021 Jun 16;21(1):581. doi: 10.1186/s12879-021-06285-3.	Background: Despite high childhood immunization coverage, sporadic cases of diphtheria have been reported in Malaysia in recent years. This study aims to evaluate the seroprevalence of diphtheria among the Malaysian population.	●									-		C	-
922	ヒト（免疫毒性）	Zasada, A. A.; Rastawicki, W.; Rokosz, N.; Jagielski, M.	Seroprevalence of diphtheria toxoid IgG antibodies in children, adolescents and adults in Poland	2020	BMC Infect Dis. 2013 Nov 19;13:551. doi: 10.1186/1471-2334-13-551.	BACKGROUND: Recommendations for diphtheria immunization are to apply an effective primary immunization in infancy and to maintain immunity throughout life. Immunity against diphtheria depends primarily on antibody to the diphtheria toxin. This study evaluated the seroprevalence of IgG diphtheria antitoxin in sera of healthy children, adolescents and adults in Poland.METHODS: A total of 1387 serum samples collected between 2010 and 2012 from individuals with ages ranging from 1 month to 85 years were investigated. Antibody concentrations were measured with an enzyme-linked immunosorbent assay (Anti-Diphtheria Toxoid ELISA IgG, Euroimmun, Germany).RESULTS: The results showed that among 1387 individuals examined, 547 -0.394 had anti-diphtheria toxoid IgG antibody levels below 0.1 IU/ml (36.9% ≤ 18 years and 0.405 >18 years old, respectively). The 212 -0.508 children and 542 -0.559 adults showed only basic protection (0.1-1.0 IU/ml) and need immediate booster. High levels of anti-diphtheria toxoid IgG antibodies (>1.0 IU/ml) were found more often in children and adolescent -0.122 than in adults -0.036 and this was statistically significant (P < 0.05). The proportion of seronegatives (< 0.1 IU/ml) in children below 2 years old, adolescents and young adults to 25 years old decreased from 0.535 to 17.4%. However, in older individuals the seronegative proportion tended to increase with age, from 0.227 in adults (26-30 years old) to 0.671 in subjects > 60 years old. Characteristically, in individuals > 40 years old high levels of anti-diphtheria toxoid IgG antibodies (>1.0 IU/ml) were not seen. There were no statistically significant differences in results in relation to gender.CONCLUSIONS: The present study showed inadequate immunity levels to diphtheria amongst the Polish population, especially in adults > 40 years old and children ≤ 2 years old. To prevent reemergence of diphtheria an information campaign reminding people about recommendations concerning diphtheria booster vaccination in adults should be conducted. Moreover, the immunogenicity of the DTP vaccine used in Poland should be verified.	●	●								-		C	-
923	ヒト（免疫毒性）	Zeng, X.; Chen, Q.; Zhang, X.; Li, H.; Liu, Q.; Li, C.; Ma, M.; Zhang, J.; Zhang, W.; Zhang, J.; Huang, L.	Association between prenatal exposure to perfluoroalkyl substances and asthma-related diseases in preschool children	2019	Environ Sci Pollut Res Int. 2019 Oct;26(29):29639-29648. doi: 10.1007/s11356-019-05864-x. Epub 2019 Aug 10.	Thus far, the few studies on the associations between perfluoroalkyl substances (PFASs) and asthma in children have yielded inconsistent results. In this study, we aimed to evaluate whether and to what extent prenatal PFASs exposure is associated with childhood asthmatic diseases. Eight PFASs were measured in cord blood drawn from 358 children in the Shanghai Allergy Birth Cohort, and a 5-year follow-up plan was completed. Asthma was diagnosed and reported by pediatric respiratory physicians via repeated symptoms (wheezing and coughing) and laboratory examination (Immunoglobulin E level test and skin prick test). A total of 0.266 and 0.174 subjects were diagnosed with wheezing and asthma, respectively. Multivariable logistic regression and piecewise linear regression were applied, and no association was found between PFASs and asthma or wheezing. However, cord serum PFOA, PFOS, and PFDA were positively correlated with serum total IgE in 5-year-old children as the level of the former beyond the turning point (4.37 ng/mL, 2.95 ng/mL, and 0.42 ng/mL, respectively), but negatively with IgE before it reach turnning point.	●	●								-		B	-
924	ヒト（免疫毒性）	Zeng, X. W.; Bloom, M. S.; Dharmage, S. C.; Lodge, C. J.; Chen, D.; Li, S.; Guo, Y.; Roponen, M.; Jalava, P.; Hirvonen, M. R.; Ma, H.; Hao, Y. T.; Chen, W.; Yang, M.; Chu, C.; Li, Q. Q.; Hu, L. W.; Liu, K. K.; Yang, B. Y.; Liu, S.; Fu, C.; Dong, G. H.	Prenatal exposure to perfluoroalkyl substances is associated with lower hand, foot and mouth disease viruses antibody response in infancy: Findings from the Guangzhou Birth Cohort Study	2019	Sci Total Environ. 2019 May 1;663:60-67. doi: 10.1016/j.scitotenv.2019.01.325. Epub 2019 Jan 26.	BACKGROUND: Perfluoroalkyl substances (PFASs) are synthetic chemicals widely used in industry and for commercial products. Their immunomodulatory effects are a growing health concern in children. Hand, Foot and Mouth Disease (HFMD) is a common childhood viral infection, and increased incidence of which has parallel the rise in PFAS exposure in the Asia-Pacific region.OBJECTIVE: We conducted the first study to assess whether prenatal exposure to PFAS was associated with a reduction in HFMD virus antibodies in infants.METHODS: We enrolled 201 mother-infant pairs from the Guangzhou Birth Cohort Study from July to October 2013 High performance liquid chromatography-mass spectrometry was employed to determine concentrations of specific PFAS isomers in cord blood. Neutralizing antibodies titers were measured against two HFMD viruses, enterovirus 71 (EV71) and coxsackievirus A 16 (CA16), in cord blood serum and blood serum at three months of age.RESULTS: Higher umbilical cord blood PFAS concentrations were associated with lower EV71 and CA16 antibody concentrations. A doubling in the composite sum of cord blood PFASs in three month old infants was associated with significant increase in the risk of HFMD antibody concentration below clinical protection level (≥1:8 titers) for CA16 (odds ratio, OR: 2.74 [95% confidence interval (CI): 1.33, 5.61] and for EV71 (OR = 4.55, 0.95 CI: 1.45, 4.28). This association was higher in boys at three months of age for CA16.CONCLUSIONS: Our findings suggest that cord blood PFAS exposure is associated with lower HFMD antibody in infancy. Given the widespread nature of PFAS exposures and the high global incidence of HFMD globally, these findings have substantial public health implications and therefore, these associations need to be replicated in a larger study to more definitively address the risk.	●	●	●					●		-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献ラン①抽出	文献ラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
925	ヒト（免疫毒性）	Zeng, X. W.; Li, Q. Q.; Chu, C.; Ye, W. L.; Yu, S.; Ma, H.; Zeng, X. Y.; Zhou, Y.; Yu, H. Y.; Hu, L. W.; Yang, B. Y.; Dong, G. H.	Alternatives of perfluoroalkyl acids and hepatitis B virus surface antibody in adults: Isomers of C8 Health Project in China	2020	Environ Pollut. 2020 Apr;259:113857. doi: 10.1016/j.envpol.2019.113857. Epub 2019 Dec 27.	Previous epidemiological and experimental studies have shown that legacy perfluoroalkyl acids (PFAAs) are immunotoxic. However, whether the immunosuppressive effects in PFAA alternatives which recently have been widely detected in the environment are unknown. To address this knowledge gap, we investigated the relationship of serum legacy PFAAs and PFAA alternatives with the antibody of hepatitis B virus in adults. We recruited 605 participants from a cross-sectional study, the Isomer of C8 Health Project in China. We measured two representative legacy PFAAs (perfluorooctane sulfonate, PFOS and perfluorooctanoic acid, PFOA), and three PFAA alternatives (two chlorinated polyfluorinated ether sulfonic acids, Cl-PFESAs and perfluorobutanoic acid, PFBA) in serum using ultra-performance liquid chromatograph-tandem mass spectrometry (UPLC-MS/MS). We applied linear and logistic regression models to analyze associations between serum PFAAs and hepatitis B surface antibody (HBsAb) with multivariable adjustments. We found negative associations between serum PFAAs concentrations and HBsAb. Lower serum HBsAb levels (log mIU/mL) were observed for each log-unit increase in linear PFOS (β = -0.31, 95% confidential interval: 0.84, -0.18), 6:2 PFESA (β = -0.81, 95% CI: 1.20, -0.42), 8:2 PFESA (β = -0.29, 95% CI: 0.43, -0.14) and PFBA (β = -0.18, 95% CI: 0.28, -0.08). The association between PFAAs and HBsAb seronegative seemed to be higher for 6:2 PFESA (odds ratio = 3.32, 95% CI: 2.16, 5.10) than its predecessors, linear PFOS (OR = 1.96, 95% CI: 1.37, 2.81) and branched PFOS isomers (OR = 1.64, 95% CI: 1.05, 2.56). We report new evidence that exposure to PFAA alternatives are associated with lower HBsAb in adults. This association seems to be stronger in 6:2 PFESA than PFOS. Our results suggest that more studies are needed to clarify the potential toxicity of PFAA alternatives in human which will facilitate better chemical regulations for PFAAs.	●	●								-		B	-
926	ヒト（免疫毒性）	Zhou, Y.; Bao, W. W.; Qian, Z. M.; Dee Geiger, S.; Parrish, K. L.; Yang, B. Y.; Lee, Y. L.; Dong, G. H.	Perfluoroalkyl substance exposure and urine CC16 levels among asthmatics: A case-control study of children	2017	Environ Res. 2017 Nov;159:158-163. doi: 10.1016/j.envres.2017.08.005. Epub 2017 Sep 18.	BACKGROUND: Studies have reported an association between serum perfluoroalkyl substances (PFASs) and asthma. However, few studies have examined the possible associations between PFASs and the 16-kDa club cell secretory protein (Clara) (CC16) level, a prominent biomarker of asthma, among adolescents.METHODS: We recruited a total of 231 asthmatic children and 225 non-asthmatic controls in the Genetic and Biomarkers study for Childhood Asthma (GBCA) in northern Taiwan from 2009 to 2010 Structured questionnaires were administered by face-to-face interview. Urine CC16 was determined by an enzyme-link immunoassay kit. Multiple general linear models were employed to examine the associations between PFASs and urinary CC16 levels.RESULTS: Asthmatic participants had significantly higher serum PFAS concentrations overall than the healthy controls. After adjusting for confounding factors, urinary CC16 was significantly, negatively associated with PFASs, especially PFOS, PFOA, PFDA and PFNA, and especially among males, as follows: PFOS (β = -0.003, 0.95 confidence interval [CI]: -0.004, -0.002), PFOA (β = -0.045, 0.95 CI: -0.086, -0.004), and PFHxA (β = -0.310, 0.95 CI: -0.455, -0.165) among asthmatic boys, and PFDA (β = -0.126, 95%CI: -0.241, -0.012) and PFNA (β = -0.329, 0.95 CI: -0.526, -0.132) among non-asthmatic boys. Among girls, PFDA (β = -0.088, 0.95 CI: -0.172, -0.004), was the only PFAS significantly associated with CC16. Significant interaction effects (p < 0.15) on CC16 levels were found between asthma and PFOS, PFOA, PFBS and PFHxA in all participants.CONCLUSION: Our overall results showed that serum PFASs were significantly, inversely associated with CC16 levels. Associations were stronger among males.	●	●								-		B	-
927	ヒト（免疫毒性）	Zhu, Y.; Qin, X. D.; Zeng, X. W.; Paul, G.; Morawska, L.; Su, M. W.; Tsai, C. H.; Wang, S. Q.; Lee, Y. L.; Dong, G. H.	Associations of serum perfluoroalkyl acid levels with T-helper cell-specific cytokines in children: By gender and asthma status	2016	Sci Total Environ. 2016 Jul 15;559:166-173. doi: 10.1016/j.scitotenv.2016.03.187. Epub 2016 Apr 6.	Perfluoroalkyl acids (PFAAs) are a group of common chemicals that ubiquitously exist in wildlife and humans. Experimental data suggest that they may alter T-lymphocyte functioning in situ by preferentially enhancing the development of T-helper 2 (TH2)- and inhibiting TH1-lymphocyte development and might increase allergic inflammation, but few human studies have been conducted. To evaluate the association between serum PFAAs concentrations and T-lymphocyte-related immunological markers of asthma in children, and further to assess whether gender modified this association, 231 asthmatic children and 225 non-asthmatic control children from Northern Taiwan were recruited into the Genetic and Biomarker study for Childhood Asthma. Serum concentrations of ten PFAAs and levels of TH1 [interferon (IFN)-γ, interleukin (IL)-2] and TH2 (IL-4 and IL-5) cytokines were measured. The results showed that asthmatics had significantly higher serum PFAAs concentrations compared with the healthy controls. When stratified by gender, a greater number of significant associations between PFAAs and asthma outcomes were found in males than in females. Among males, adjusted odds ratios for asthma among those with the highest versus lowest quartile of PFAAs exposure ranged from 2.59 (95% CI: 1.14, 5.87) for the perfluorobutanesulfonate (PFBS) to 4.38 (95% CI: 2.02, 9.50) for perfluorooctanesulfonate (PFOS); and serum PFAAs were associated positively with TH2 cytokines and inversely with TH1 cytokines among male asthmatics. Among females, no significant associations between PFAAs and TH2 cytokines could be detected. In conclusion, increased serum PFAAs levels may promote TH cell dysregulation and alter the availability of key TH1 and TH2 cytokines, ultimately contributing to the development of asthma that may differentially impact males to a greater degree than females. These results have potential relevance in asthma prevention.	●	●		●				●		-		B	-
928	ヒト（免疫毒性）	Ashley-Martin, Jillian; Dodds, Linda; Levy, Adrian R; Platt, Robert W; Marshall, Jean S; Arbuckle, Tye E	Prenatal exposure to phthalates, bisphenol A and perfluoroalkyl substances and cord blood levels of IgE, TSLP and IL-33	2015	Environ Res. 2015 Jul;140:360-8. doi: 10.1016/j.envres.2015.04.010. Epub 2015 Apr 24.	The fetal time period is a critical window of immune system development and resulting heightened susceptibility to the adverse effects of environmental exposures. Epidemiologists and toxicologists have hypothesized that phthalates, bisphenol A (BPA) and perfluoroalkyl substance have immunotoxic properties. Immunotoxic effects of chemicals may manifest in an altered immune system profile at birth. Immunoglobulin E, thymic stromal lymphopoietin (TSLP), and interleukin-33 (IL-33) are integral in the etiology of childhood allergy and detectable at birth. The objective of this study was to determine the association between maternal levels of phthalates, bisphenol A (BPA), and perfluoroalkyl substances and elevated umbilical cord blood levels of IgE, TSLP, and IL-33. This study utilized data collected in the Maternal-Infant Research on Environmental Chemicals (MIREC) Study, a trans-Canada cohort study of 2001 pregnant women. Of these women, 1258 had a singleton, term birth and cord blood sample. A Bayesian hierarchical model was employed to determine associations between log-transformed continuous variables and immune system biomarkers while adjusting for potential confounding from correlated environmental contaminants. Inverse, nonlinear associations were observed between maternal urinary MCPP levels and elevated levels of both IL-33/TSLP and IgE and between maternal urinary BPA levels and elevated levels of IL-33/TSLP. In this primarily urban Canadian population of pregnant women and their newborns, maternal urinary and plasma concentrations of phthalate metabolites, BPA, and perfluoroalkyl substances were not associated with immunotoxic effects that manifest as increased odds of elevated levels of IgE, TSLP or IL-33.			●	●						-		C	-
929	ヒト（免疫毒性）	Fei, Chunyuan; McLaughlin, Joseph K; Lipworth, Loren; Olsen, Jørn	Prenatal exposure to PFOA and PFOS and risk of hospitalization for infectious diseases in early childhood	2010	Environ Res. 2010 Nov;110(8):773-7. doi: 10.1016/j.envres.2010.08.004. Epub 2010 Aug 30.	OBJECTIVES: To examine whether prenatal exposure to perfluorooctanesulfonate (PFOS) or perfluorooctanoate (PFOA) is associated with the occurrence of hospitalization for infectious diseases during early childhood. METHODS: We randomly selected 1400 pregnant women and their offspring from the Danish National Birth Cohort (1996-2002) and measured PFOS and PFOA levels in maternal blood during early pregnancy. Hospitalizations for infection of the offspring were identified by the linkage to the National Hospital Discharge Register through 2008. RESULTS: Hospitalizations due to infections were not associated with prenatal exposure to PFOA and PFOS. On the contrary, the relative risks of hospitalizations ranged from 0.71 to 0.84 for the three higher quartiles of maternal PFOA levels compared with the lowest, but no dose-response pattern was found. No clear pattern was observed when results were stratified by child's age at infection, with the exception of an inverse association between maternal PFC levels and risk of hospitalization during the child's first year of life. CONCLUSIONS: These findings suggest that prenatal exposure to PFOA or PFOS is not associated with increased risk of infectious diseases leading to hospitalization in early childhood.			●	●	●	●				-		B	-
930	ヒト（免疫毒性）	Okada, Emiko; Sasaki, Seiko; Kashino, Ikuko; Matsuura, Hideyuki; Miyashita, Chihiro; Kobayashi, Sumitaka; Itoh, Kumiko; Ikeno, Tamiko; Tamakoshi, Akiko; Kishi, Reiko	Prenatal exposure to perfluoroalkyl acids and allergic diseases in early childhood	2014	Environ Int. 2014 Apr;65:127-34. doi: 10.1016/j.envint.2014.01.007. Epub 2014 Jan 29.	Perfluoroalkyl acids (PFAAs) are persistent organic pollutants that are detected in humans worldwide. Laboratory animal studies have shown that PFAAs are associated with immunotoxic effects. However, epidemiological studies investigating the role of PFAAs, in particular PFAAs with longer chains than perfluorooctanoic acid, are scarce. We investigated associations between prenatal exposure to PFAAs, including long-chain compounds, and infant allergic diseases at 12 and 24months in a large study population. The participants included mothers and their infants who enrolled in the Hokkaido Study on Environment and Children's Health 2003-2009. Eleven PFAAs were measured in maternal plasma taken at 28-32weeks of gestation using ultra-performance liquid chromatography coupled to triple quadrupole tandem mass spectrometry. Characteristics of participants and information on infant allergic diseases were obtained from self-administered questionnaires and medical records. At 24months, the adjusted odds ratio (OR) (first vs. fourth quartiles) for eczema in association with higher maternal perfluorotridecanoic acid (PFTrDA) levels was 0.62 (95% confidence interval (CI) 0.45, 0.86). After stratification by gender, the adjusted ORs in female infants from mothers with higher maternal perfluoroundecanoic acid (PFUnDA) and PFTrDA levels were also statistically significant (PFUnDA: OR=0.50; 95% CI, 0.30, 0.81; PFTrDA: OR=0.39; 95% CI, 0.23, 0.64). Our findings suggest that lower prenatal exposure to PFTrDA may decrease the risk of developing eczema in early childhood, only in female infants.			●	●						-		B	-
931	ヒト（免疫毒性）	Stein, Cheryl R; McGovern, Kathleen J; Pajak, Ashley M; Maglione, Paul J; Wolff, Mary S	Perfluoroalkyl and polyfluoroalkyl substances and indicators of immune function in children aged 12-19 y: National Health and Nutrition Examination Survey	2016	Pediatr Res. 2016 Feb;79(2):348-57. doi: 10.1038/pr.2015.213. Epub 2015 Oct 22.	BACKGROUND: Perfluoroalkyl and polyfluoroalkyl substances (PFAS) are immunotoxic in laboratory studies. Human studies of immune effects are inconsistent. Using the US National Health and Nutrition Examination Survey (NHANES), we examined PFAS serum concentration and indicators of prevalent immune function among 12-19-y-old children. METHODS: In this cross-sectional study, we examined PFAS serum concentration in relation to measles, mumps, and rubella antibody concentrations in NHANES 1999-2000 and 2003-2004 (n = 1,191) and to allergic conditions and allergic sensitization in NHANES 2005-2006 (n = 640). RESULTS: In adjusted, survey-weighted models, a doubling of perfluorooctane sulfonate (PFOS) concentration among seropositive children was associated with a 13.3% (95% confidence interval (CI): -19.9, -6.2) decrease in rubella antibody concentration and a 5.9% decrease in mumps antibody concentration (95% CI: -9.9, -1.6). We observed no adverse association between exposure and current allergic conditions, including asthma. Children with higher PFOS concentration were less likely to be sensitized to any allergen (odds ratio (OR): 0.74; 95% CI: 0.58, 0.95). CONCLUSION: Increased exposure to several PFAS was associated with lower levels to mumps and rubella antibody concentrations, especially among seropositive individuals. These lower antibody concentrations may indicate a less robust response to vaccination or greater waning of vaccine-derived immunity over time.			●	●				●		-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
932	ヒト（免疫毒性）	Tao, Lin; Kannan, Kurunthachalam; Aldous, Kenneth M; Mauer, Matthew P; Eadon, George A	Biomonitoring of perfluorochemicals in plasma of New York State personnel responding to the World Trade Center disaster	2008	Environ Sci Technol. 2008 May 1;42(9):3472-8. doi: 10.1021/es8000079.	The collapse of the World Trade Center (WTC) on September 11, 2001 resulted in the release of several airborne pollutants in and around the site. Perfluorochemicals including perfluorooctanesulfonate (PFOS) and perfluorooctanoic acid (PFOA), which are used in soil- and stain-resistant coatings on upholstery, carpets, leather, floor waxes, polishes, and in fire-fighting foams were potentially released during the collapse of the WTC. In this pilot study, we analyzed 458 plasma samples of New York State (NYS) employees and National Guard personnel assigned to work in the vicinity of the WTC between September 11 and December 23, 2001, to assess exposure to perfluorochemicals released in dust and smoke. The plasma samples collected from NYS WTC responders were grouped based on estimated levels of exposure to dust and smoke, as follows: more dust exposure (MDE), less dust exposure (LDE), more smoke exposure (MSE), and less smoke exposure (LSE). Furthermore, samples were grouped, based on self-reported symptoms at the time of sampling, as symptomatic and asymptomatic. Eight perfluorochemicals were measured in 458 plasma samples. PFOS, PFOA, perfluorohexanesulfonate (PFHxS), and perfluorononanoic acid (PFNA), were consistently detected in almost all samples. PFOA and PFHxS concentrations were approximately 2-fold higher in WTC responders than the concentrations reported for the U.S. general population. No significant difference was observed in the concentrations of perfluorochemicals between symptomatic and asymptomatic groups. Concentrations of PFHxS were significantly (p < or = 0.05) higher in the MDE group than in the LDE group. Concentrations of PFNA were significantly higher in the MSE group than in the LSE group. Significantly higher concentrations of PFOA and PFHxS were found in individuals exposed to smoke than in individuals exposed to dust. A significant negative correlation existed between plasma lipid content and concentrations of certain perfluorochemicals. Our initial findings suggest that WTC responders were exposed to perfluorochemicals, especially PFOA, PFNA, and PFHxS, through inhalation of dust and smoke released during and after the collapse of the WTC. The potential health implications of these results are unknown at this time. Expansion of testing to include all archived samples will be critical to help confirm these findings. In doing so, it may be possible to identify biological markers of WTC exposure and to improve our understanding of the health impacts of these compounds.			●	●						-		C	-
933	ヒト（免疫毒性）	Wang, I-Jen; Hsieh, Wu-Shiun; Chen, Chia-Yang; Fletcher, Tony; Lien, Guang-Wen; Chiang, Hung-Lung; Chiang, Chow-Feng; Wu, Trong-Neng; Chen, Pau-Chung	The effect of prenatal perfluorinated chemicals exposures on pediatric atopy	2011	Environ Res. 2011 Aug;111(6):785-91. doi: 10.1016/j.envres.2011.04.006. Epub 2011 May 23.	BACKGROUND: The role of perfluorinated compounds (PFCs) in the immune system and allergic diseases is not well-known. This study examined the effects of pre-natal exposure to PFCs on immunoglobulin E (IgE) levels and atopic dermatitis (AD). METHODS: In Taiwan Birth Panel cohort study, newborns with cord blood and peri-natal factors (i.e. birth body weight, weeks of gestation, and type of delivery) gathered at birth were evaluated. At the age of 2 years, information on the development of AD, environmental exposures, and serum total IgE were collected. The AD and non-AD children were compared for the concentration of cord blood serum PFCs measured by Ultra-performance liquid chromatography/triple-quadrupole mass (UPLC-MS/MS). Correlations among cord blood IgE, serum total IgE at 2 years of age, and cord blood PFC levels were made. RESULTS: Of 244 children who completed the follow-up and specimen collections, 43 (17.6%) developed AD. Concentrations of cord blood serum perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), perfluorononanoic acid (PFNA), and perfluorohexane sulfonic acid (PFHxS) were median (range) 1.71 (0.75-17.40), 5.50 (0.11-48.36), 2.30 (0.38-63.87), and 0.035 (0.035-0.420)ng/mL, respectively. PFOA and PFOS levels positively correlated with cord blood IgE levels (per ln-unit: β=0.134 KU/l, p=0.047 for PFOA; β=0.161 KU/l, p=0.017 for PFOS). Analyses stratified by gender revealed that PFOA and PFOS levels positively correlated with cord blood IgE levels only in boys (per ln-unit: β=0.206 KU/l, p=0.025 for PFOA; β=0.175 KU/l, p=0.053 for PFOS). When dividing cord blood serum PFCs into quartiles in the fully adjusted models, AD had no significant association with PFOS. CONCLUSIONS: Pre-natal PFOA and PFOS exposures positively correlated with cord blood IgE levels.			●	●						-		B	-
934	ヒト（免疫毒性）	Grandjean P, Andersen EW, Budtz-Jørgensen E, Nielsen F, Mølbak K, Weihe P, Heilmann C.	Serum vaccine antibody concentrations in children exposed to perfluorinated compounds	2012	JAMA. 2012 Jan 25;307(4):391-7. doi: 10.1001/jama.2011.2034.	Context: Perfluorinated compounds (PFCs) have emerged as important food contaminants. They cause immune suppression in a rodent model at serum concentrations similar to those occurring in the US population, but adverse health effects of PFC exposure are poorly understood. Objective: To determine whether PFC exposure is associated with antibody response to childhood vaccinations. Design, setting, and participants: Prospective study of a birth cohort from the National Hospital in the Faroe Islands. A total of 656 consecutive singleton births were recruited during 1997-2000, [corrected] and 587 participated in follow-up through 2008. Main outcome measures: Serum antibody concentrations against tetanus and diphtheria toxoids at ages 5 and 7 years. Results: Similar to results of prior studies in the United States, the PFCs with the highest serum concentrations were perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA). Among PFCs in maternal pregnancy serum, PFOS showed the strongest negative correlations with antibody concentrations at age 5 years, for which a 2-fold greater concentration of exposure was associated with a difference of -39% (95% CI, -55% to -17%) in the diphtheria antibody concentration. PFCs in the child's serum at age 5 years showed uniformly negative associations with antibody levels, especially at age 7 years, except that the tetanus antibody level following PFOS exposure was not statistically significant. In a structural equation model, a 2-fold greater concentration of major PFCs in child serum was associated with a difference of -49% (95% CI, -67% to -23%) in the overall antibody concentration. A 2-fold increase in PFOS and PFOA concentrations at age 5 years was associated with odds ratios between 2.38 (95% CI, 0.89 to 6.35) and 4.20 (95% CI, 1.54 to 11.44) for falling below a clinically protective level of 0.1 IU/mL for tetanus and diphtheria antibodies at age 7 years. Conclusion: Elevated exposures to PFCs were associated with reduced humoral immune response to routine childhood immunizations in children aged 5 and 7 years.				●				●		-		B	-
935	ヒト（免疫毒性）	Heilmann, Carsten; Budtz-Jørgensen, Esben; Nielsen, Flemming; Heinzow, Birger; Weihe, Pál; Grandjean, Philippe	Serum concentrations of antibodies against vaccine toxoids in children exposed perinatally to immunotoxicants	2010	Environ Health Perspect. 2010 Oct;118(10):1434-8. doi: 10.1289/ehp.1001975. Epub 2010 Jun 1.	BACKGROUND: Polychlorinated biphenyls (PCBs) may cause immunotoxic effects, but the detailed dose-response relationship and possible vulnerable time windows of exposure are uncertain. In this study we applied serum concentrations of specific antibodies against childhood vaccines as sentinels of immunotoxicity. OBJECTIVES: The main objective was to assess the possible dependence of antibody concentrations against diphtheria and tetanus toxoids in children with regard to prenatal and postnatal PCB exposures. METHODS: From a cohort of 656 singleton births formed in the Faroe Islands during 1999-2001, children were invited for examination with assessment of serum antibody concentrations at 5 years (before and after a booster vaccination) and at 7 years of age. Total PCB concentrations were determined in serum from ages 5 and 7 years, and data were also available on PCB concentrations in maternal pregnancy serum, maternal milk, and, for a subgroup, the child's serum at 18 months of age. RESULTS: A total of 587 children participated in the examinations at ages 5 and/or 7 years. At age 5 years, before the booster vaccination, the antidiphtheria antibody concentration was inversely associated with PCB concentrations in milk and 18-month serum. Results obtained 2 years later showed an inverse association of concentrations of antibodies against both toxoids with PCB concentrations at 18 months of age. The strongest associations suggested a decrease in the antibody concentration by about 20% for each doubling in PCB exposure. At age 5 years, the odds of an antidiphtheria antibody concentration below a clinically protective level of 0.1 IU/L increased by about 30% for a doubling in PCB in milk and 18-month serum. CONCLUSIONS: Developmental PCB exposure is associated with immunotoxic effects on serum concentrations of specific antibodies against diphtheria and tetanus vaccinations. The immune system development during the first years of life appears to be particularly vulnerable to this exposure.				●				●		-		C	-
936	ヒト（免疫毒性）	Osuna, Christa E; Grandjean, Philippe; Weihe, Pál; El-Fawal, Hassan A N	Autoantibodies associated with prenatal and childhood exposure to environmental chemicals in Faroese children	2014	Toxicol Sci. 2014 Nov;142(1):158-66. doi: 10.1093/toxsci/kfu163. Epub 2014 Aug 14.	Methylmercury, polychlorinated biphenyls (PCBs), and perfluorinated compounds (PFCs) are ubiquitous and persistent environmental chemicals with known or suspected toxic effects on the nervous system and the immune system. Animal studies have shown that tissue damage can elicit production of autoantibodies. However, it is not known if autoantibodies similarly will be generated and detectable in humans following toxicant exposures. Therefore, we conducted a pilot study to investigate if autoantibodies specific for neural and non-neural antigens could be detected in children at age 7 years who have been exposed to environmental chemicals. Both prenatal and age-7 exposures to mercury, PCBs, and PFCs were measured in 38 children in the Faroe Islands who were exposed to widely different levels of these chemicals due to their seafood-based diet. Concentrations of IgM and IgG autoantibodies specific to both neural (neurofilaments, cholineacetyltransferase, astrocyte glial fibrillary acidic protein, and myelin basic protein) and non-neural (actin, desmin, and keratin) antigens were measured and the associations of these autoantibody concentrations with chemical exposures were assessed using linear regression. Age-7 blood-mercury concentrations were positively associated with titers of multiple neural- and non-neural-specific antibodies, mostly of the IgM isotype. Additionally, prenatal blood-mercury and -PCBs were negatively associated with anti-keratin IgG and prenatal PFOS was negatively associated with anti-actin IgG. These exploratory findings demonstrate that autoantibodies can be detected in the peripheral blood following exposure to environmental chemicals. The unexpected association of exposures with antibodies specific for non-neural antigens suggests that these chemicals may have toxicities that have not yet been recognized.				●						-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ラン①	文献ラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
937	ヒト（免疫毒性）	Bramer, CA; Kimmins, LM; Swanson, R; Kuo, J; Vranesich, P; Jacques-Carroll, LA; Shen, AK.	Decline in Child Vaccination Coverage During the COVID-19 Pandemic - Michigan Care Improvement Registry, May 2016-May 2020	2020	MMWR Morb Mortal Wkly Rep. 2020 May 22;69(20):630-631. doi: 10.15585/mmwr.mm6920e1.	On March 13, 2020, the United States declared a national state of emergency to control the pandemic spread of SARS-CoV-2, the virus that causes coronavirus disease 2019 (COVID-19) (1). Public health response measures to mitigate the pandemic have centered on social distancing and quarantine policies, including shelter-in-place and stay-at-home orders. Michigan implemented a stay-at-home order on March 23, 2020, to facilitate social distancing (2). Such strategies might result in decreased accessibility to routine immunization services, leaving children at risk for vaccine-preventable diseases and their complications (3). To evaluate whether vaccination coverage has changed during the pandemic, data from the Michigan Care Improvement Registry (the state's immunization information system) (MCIR) were analyzed. Changes in vaccine doses administered to children and the effects of those changes on up-to-date status were examined for vaccinations recommended at milestone ages corresponding to the end of an Advisory Committee on Immunization Practices (ACIP) recommendation period for one or more vaccines (4).		●								-		C	-
938	ヒト（免疫毒性）	WHO	Tetanus vaccines: WHO position paper - February 2017	2017	Wkly Epidemiol Rec. 2017 Feb 10;92(6):53-76.	No abstract available		●							WHO position paper		C	-
939	ヒト（免疫毒性）	C8 Science Panel	Probable link evaluations for autoimmune disease, infectious disease, neurodevelopmental disorders in children, respiratory disease, stroke, and thyroid disease	2012	C8 probable link reports, http://www.c8sciencepanel.org/prob_link.html	No abstract available						●			C8 science panel ウェブサイト公表資料。対象外とする		C	-
940	ヒト（免疫毒性）	Dalsager, L.; Christensen, N.; Halekoh, U.; Timmermann, C. A. G.; Nielsen, F.; Kyhl, H. B.; Husby, S.; Grandjean, P.; Jensen, T. K.; Andersen, H. R.	Exposure to perfluoroalkyl substances during fetal life and hospitalization for infectious disease in childhood: A study among 1,503 children from the Odense Child Cohort.	2021	Environ Int. 2021 Apr;149:106395. doi: 10.1016/j.envint.2021.106395. Epub 2021 Jan 25.	INTRODUCTION: The immunosuppressive properties of PFASs are widely recognized. Early-life exposure to PFAS has been linked to reduced immune response to childhood vaccinations and increased rates of common infectious diseases, but implications for hospitalizations are unclear.OBJECTIVES: To investigate the association between maternal serum concentrations of five PFASs during pregnancy and the child's rate of hospitalization due to common infectious diseases between birth and 4 years of age.METHODS: Serum samples from first trimester pregnant women from the Odense Child Cohort (OCC) collected in 2010-2012 were analyzed for concentrations of perfluorooctanesulfonic acid (PFOS), perfluorooctanoic acid (PFOA) and three other PFASs. Data on child hospitalizations with an ICD-10 code for infectious disease was obtained from the Danish National Patient Register. The following were identified: upper respiratory tract infections (URTI), lower respiratory tract infections (LRTI), gastrointestinal infections (GI), and other infections. The Andersen-Gill Cox proportional hazard model for recurrent events was used to investigate the association between PFAS exposure and hospitalizations. The resulting estimates were hazard ratios (HRs), which express the relative change in the instantaneous risk of hospitalization with a doubling in maternal PFAS concentration.RESULTS: A total of 1503 mother-child pairs were included, and 0.26 of the children were hospitalized at least once for infectious disease. A doubling in maternal PFOS concentration was associated with a 0.23 increase in the risk of hospitalization due to any infection (HR: 1.23 (95% CI: 1.05, 1.44). There was indication of an interaction between child sex and PFOS (p = 0.07) and PFDA (p = 0.06), although in opposite directions. Further, every doubling of PFOA or PFOS increased the risk of LRTI by 0.27 (HR: 1.27 (1.01, 1.59)) and 0.54 (HR: 1.54 (1.11, 2.15)), respectively. Similar tendencies were seen for URTI and the group of other infections. For GIs, the opposite pattern of association was seen as HR's were consistently below 1 (PFOA, HR: 0.55 (0.32, 0.95)).DISCUSSION: We found an association between PFOS and the overall risk of infectious disease, and between PFOS and PFOA exposures and the risk of LRTI's. These results are in agreement with previous findings from the OCC, in which maternal PFOS and PFOA concentrations were positively associated with the number of days that the children experienced fever, thereby suggesting that PFOS and PFOA may affect the prevalence of both mild and more severe infectious diseases even in a rather low-exposed population.							●			-	1	A	-
941	ヒト（免疫毒性）	Fenton, S. E.; Ducatman, A.; Boobis, A.; DeWitt, J. C.; Lau, C.; Ng, C.; Smith, J. S.; Roberts, S. M.	Per- and polyfluoroalkyl substance toxicity and human health review: Current state of knowledge and strategies for informing future research.	2021	Environ Toxicol Chem. 2021 Mar;40(3):606-630. doi: 10.1002/etc.4890.	Reports of environmental and human health impacts of per- and polyfluoroalkyl substances (PFAS) have greatly increased in the peer-reviewed literature. The goals of this review are to assess the state of the science regarding toxicological effects of PFAS, and to develop strategies for advancing knowledge on the health effects of this large family of chemicals. Currently, much of the toxicity data available for PFAS are for a handful of chemicals, primarily legacy PFAS such as perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS). Epidemiological studies have revealed associations between exposure to specific PFAS and a variety of health effects, including altered immune and thyroid function, liver disease, lipid and insulin dysregulation, kidney disease, adverse reproductive and developmental outcomes, and cancer. Concordance with experimental animal data exists for many of these effects. However, information on modes of action and adverse outcome pathways must be expanded, and profound differences in PFAS toxicokinetic properties must be considered in understanding differences in responses between sexes and among species and life stages. With many health effects noted for a relative few example compounds, and hundreds of other PFAS in commerce lacking toxicity data, more contemporary and high throughput approaches such as read across, molecular dynamics, and protein modeling are proposed to accelerate the development of toxicity information on emerging and legacy PFAS, individually and as mixtures. Additionally, an appropriate degree of precaution, given what is already known from the PFAS examples noted here, may be needed to protect human health.								●		レビュー		A	-
942	ヒト（免疫毒性）	Huang, H.; Yu, K.; Zeng, X.; Chen, Q.; Liu, Q.; Zhao, Y.; Zhang, J.; Zhang, X.; Huang, L.	Association between prenatal exposure to perfluoroalkyl substances and respiratory tract infections in preschool children.	2020	Environ Res. 2020 Dec;191:110156. doi: 10.1016/j.envres.2020.110156. Epub 2020 Aug 30.	Background: Prenatal exposure to perfluoroalkyl substances (PFAS) is considered to affect adversely the immune function. However, the effect of prenatal PFAS exposure on respiratory tract infections (RTIs) in children is unclear. Thus, we evaluated whether cord blood PFAS levels were associated with RTI in the first 5 years of life.								●		-		B	-
943	ヒト（免疫毒性）	Kirk M, Smurthwaite K, Brä unig J, Trevenar S, D'Este C, Lucas R, Lal A, Korda R, Clements A, Mueller J and Armstrong B	The PFAS Health Study: Systematic Literature Review	2018	Available at http://nceph.anu.edu.au/files/PFAS%20Health%20Study%20Systematic%20Review_1.pdf	No abstract available							●		システマティックレビュー	1	A	-
944	ヒト（免疫毒性）	Antoniou, Evangelia; Colnot, Thomas; Zeegers, Maurice; Dekant, Wolfgang	Immunomodulation and exposure to per- and polyfluoroalkyl substances: an overview of the current evidence from animal and human studies	2022	Arch Toxicol. 2022 Aug;96(8):2261-2285. doi: 10.1007/s00204-022-03303-4. Epub 2022 Jun 13.	Per- and polyfluoroalkyl substances (PFAS) have been widely used and represent a class of environmental persistent chemicals. An association of a reduction of vaccination efficacy with PFAS serum levels in humans was used by the European Food Safety Authority as a key effect for PFAS risk assessment. The data support for using this association is reviewed by a critical analysis of the respective human epidemiology and the available animal studies on the immunomodulation of PFAS. Based on an analysis of the available human epidemiology, the overall level of evidence regarding associations between PFAS serum levels and reduced antibody response remains weak. Absence of an association between an increase in clinical infections and PFAS serum levels and the limited understanding of the importance of antibody levels as an isolated data point further support this conclusion. Animal toxicity studies with PFAS focusing on immunomodulation also provide only limited support for immunomodulation as an important endpoint in PFAS toxicity. While immunomodulation is observed after PFAS administration, generally at blood concentrations several orders of magnitude above those seen in environmentally exposed humans, the relevance of these observation is hampered by the high doses required to influence immune endpoints, the limited number of endpoints assessed, and inconsistent results. The limitations of the current database on associations of human PFAS exposures outlined here indicate that more evidence is required to select immunomodulation as a critical endpoint for human PFAS risk assessment.									●	-		B	-
945	ヒト（内分泌系）	Aimuzi, R.; Luo, K.; Chen, Q.; Wang, H.; Feng, L.; Ouyang, F.; Zhang, J.	Perfluoroalkyl and polyfluoroalkyl substances and fetal thyroid hormone levels in umbilical cord blood among newborns by prelabor caesarean delivery	2019	Environ Int. 2019 Sep;130:104929. doi: 10.1016/j.envint.2019.104929. Epub 2019 Jun 20.	BACKGROUND: Perfluoroalkyl and polyfluoroalkyl substances (PFAS) have been reported to disrupt the thyroid function. But epidemiological evidence on the association between PFAS and thyroid hormone (TH) levels in cord blood is scarce and controversial. We aimed to examine the association between cord blood PFAS concentrations and TH levels in prelabor caesarean deliveries.METHODS: We measured ten PFAS and three THs in cord blood in 568 prelabor caesarean deliveries. The associations between PFAS and TH levels were examined using multiple linear regression model and sparse partial least squares (SPLS) regression model.RESULTS: In SPLS analyses, thyroid stimulating hormone (TSH) level decreased with increasing concentrations of perfluorooctane sulfonate (PFOS, β = -0.012, 0.95 confidence interval [CI]: -0.019, -0.005), perfluorononanoic acid (PFNA, β = -0.012, 0.95 CI: -0.019, -0.005), perfluorodecanoic acid (PFDA, β = -0.012, 0.95 CI: -0.02, -0.005), perfluoroundecanoic acid (PFUA, β = -0.013, 0.95 CI: -0.021, -0.006) and perfluorododecanoic acid (PFDoA, β = -0.013, 0.95 CI: -0.023, -0.006). Moreover, we found a positive association between PFDoA and free thyroxine (FT4) levels (β = 0.190, 0.95 CI: 0.063, 0.304) after adjusting for potential confounders. Free tri-iodothyronine (FT3) levels were positively associated with concentrations of PFOS (β = 0.059, 0.95 CI: 0.023, 0.100), but negatively associated with PFDoA (β = -0.153, 0.95 CI: -0.212, -0.106). We also observed gender disparity in the associations of PFAS exposure and FT3, FT4, TSH levels.CONCLUSION: Our results suggest that prenatal exposure to certain PFAS may disrupt fetal thyroid function. The effect may be gender-specific.	●	●								-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
946	ヒト（内分泌系）	Aimuzi, R.; Luo, K.; Huang, R.; Huo, X.; Nian, M.; Ouyang, F.; Du, Y.; Feng, L.; Wang, W.; Zhang, J.	Perfluoroalkyl and polyfluoroalkyl substances and maternal thyroid hormones in early pregnancy	2020	Environ Pollut. 2020 Sep;264:114557. doi: 10.1016/j.envpol.2020.114557. Epub 2020 Apr 30.	BACKGROUND: The development of the embryo and fetal brain depends on maternal transfer of thyroid hormones (THs) in early pregnancy. Perfluoroalkyl and polyfluoralkyl substances (PFAS) may disrupt maternal TH homeostasis in pregnancy, but findings from epidemiologic studies were inconsistent. We aimed to assess this relationship in early pregnancy in a large prospective cohort study.METHODS: A total of 1885 pregnant women enrolled in the Shanghai Birth Cohort were used. Ten PFAS, free thyroxine (FT4), free triiodothyronine (FT3), thyroid stimulating hormone (TSH) and thyroid peroxidase antibody (TPOAb) were measured in maternal blood collected prior to 16 weeks of gestation. Multiple linear regression accompanied by restricted cubic spline was used to examine the association and the exposure-response relationship between each PFAS and TH in separate models. Possible effect modification by TPOAb status was also investigated.RESULTS: Perfluorooctanoic acid [PFOA, β = 0.121, 0.95 confidence interval (CI): 0.015, 0.227] and perfluorohexane sulfonate (PFHxS, β = 0.123, 0.95 CI: 0.024, 0.222) were positively associated with FT4. Perfluorononanoic acid (PFNA, β = 0.179, 0.95 CI: 0.047, 0.311) and PFHxS (β = 0.197, 0.95 CI: 0.054, 0.339) were positively associated with FT3, while PFHxS was negatively associated with TSH (β = -0.115, 95%CI: 0.216, -0.014). TPOAb-positivity appeared to modify the associations between PFAS and THs. In TPOAb-positive women, several long-chain PFAS were positively associated with FT4 and/or FT3 and tended to be negatively associated with TSH.CONCLUSIONS: Several long-chain PFAS were associated with disrupted TH homeostasis in Chinese pregnant women, especially among TPOAb-positive women.	●	●								-		1	B	A
947	ヒト（内分泌系）	Audet-Delage, Y.; Ouellet, N.; Dallaire, R.; Dewailly, E.; Ayotte, P.	Persistent organic pollutants and transthyretin-bound thyroxin in plasma of inuit women of childbearing age	2013	Environ Sci Technol. 2013 Nov 19;47(22):13086-92. doi: 10.1021/es4027634. Epub 2013 Nov 11.	The Inuit population of Nunavik (Northern Quebec, Canada) is highly exposed to persistent organic pollutants (POPs) through their traditional diet. Some POPs, i.e., hydroxylated metabolites of polychlorinated biphenyls (OH-PCBs), pentachlorophenol (PCP), and perfluorooctane sulfonate (PFOS), compete with thyroxin (T4) for binding sites on transthyretin (TTR), a T4 transport protein found in plasma and cerebrospinal fluid. We tested the hypothesis that these TTR-binding compounds decrease circulating concentrations of T4 bound to TTR (T4-TTR) in Inuit women of reproductive age. We measured the concentration of T4-TTR in plasma samples obtained from 120 Inuit women (18-39 years old) by combining native-polyacrylamide gel electrophoresis and liquid chromatography-tandem mass spectrometry (LC-MS/MS) techniques. Total T4, TTR, and thyroxin-binding globulin (TBG) concentrations were also determined, while POPs levels had been previously measured. The mean T4-TTR concentration was 8.4 nmol/L (SD = 2.4) with values ranging from 2.9 to 14.4 nmol/L. Linear regression analysis revealed that TTR, TBG, and total T4 concentrations were significant predictors (p < 0.002) of T4-TTR levels (total adjusted R-squared = 0.26, p < 0.0001) but not levels of OH-PCBs, chlorophenols, or PFOS. Our results suggest that circulating levels of these TTR-binding compounds in Inuit women of childbearing age are not high enough to affect TTR-mediated thyroid hormone transport. The possibility of increased delivery of these compounds to the developing brain requires further investigation.	●	●								-			C	C
948	ヒト（内分泌系）	Berg, V.; Nøst, T. H.; Hansen, S.; Elverland, A.; Veyhe, A. S.; Jorde, R.; Odland, J. Ø.; Sandanger, T. M.	Assessing the relationship between perfluoroalkyl substances, thyroid hormones and binding proteins in pregnant women; a longitudinal mixed effects approach	2015	Environ Int. 2015 Apr;77:63-9. doi: 10.1016/j.envint.2015.01.007. Epub 2015 Jan 31.	The mechanisms involved in thyroid homeostasis are complex, and perfluoroalkyl substances (PFASs) have been indicated to interfere at several levels in this endocrine system. Disruption of the maternal thyroid homeostasis during early pregnancy is of particular concern, where subclinical changes in maternal thyroid hormones (THs) may affect embryonic and foetal development. The present study investigated associations between THs, thyroid binding proteins (TH-BPs) and PFAS concentrations in pregnant women from Northern Norway. Women participating in The Northern Norway Mother-and-Child contaminant Cohort Study (MISA) donated a blood sample at three visits related to their pregnancy and postpartum period (during the second trimester, 3 days and 6 weeks after delivery) in the period 2007-2009. Participants were assigned to quartiles according to PFAS concentrations during the second trimester and mixed effects linear models were used to investigate potential associations between PFASs and repeated measurements of THs, TH-BPs, thyroxin binding capacity and thyroid peroxidase antibodies (anti-TPOs). Women within the highest perfluorooctane sulfonate (PFOS) quartile had 0.24 higher mean concentrations of thyroid stimulating hormone (TSH) compared to the first quartile at all sampling points. Women within the highest quartiles of perfluorodecanoate (PFDA) had 0.04 lower mean concentrations of triiodothyronine (T3) and women within the highest quartile of perfluoroundecanoate (PFUnDA) had 0.03 lower mean concentrations of free triiodothyronine (FT3). Further, the difference in concentrations and the changes between three time points were the same for the PFAS quartiles. Thyroxin binding capacity was associated with all the THs and TH-BPs, and was selected as a holistic adjustment for individual changes in TH homeostasis during pregnancy. Finally, adjusting for maternal iodine status did not influence the model predictions. Findings in the present study suggest modifications of TH homeostasis by PFASs in a background exposed maternal population. The variation in levels of THs between PFAS quartiles was within normal reference ranges and may not be of clinical significance in the pregnant woman. However, subtle individual changes in maternal THs may have significant consequences for foetal health.	●	●	●	●						-			B	B
949	ヒト（内分泌系）	Blake, B. E.; Pinney, S. M.; Hines, E. P.; Fenton, S. E.; Ferguson, K. K.	Associations between longitudinal serum perfluoroalkyl substance (PFAS) levels and measures of thyroid hormone, kidney function, and body mass index in the Fernald Community Cohort	2018	Environ Pollut. 2018 Nov;242(Pt A):894-904. doi: 10.1016/j.envpol.2018.07.042. Epub 2018 Jul 17.	Perfluoroalkyl substances (PFAS) are a diverse class of manufactured compounds used in a wide range of industrial processes and consumer products and have been detected in human serum worldwide. Previous cross-sectional and cohort studies in humans have suggested exposure to PFAS is associated with a wide array of chronic diseases, including endocrine disruption, developmental health effects, cancer and metabolic changes. We examined the associations between a panel of eight PFAS and indicators of thyroid disruption, kidney function, and body mass index (BMI), all of which were measured at repeated time points (1990-2008) over the course of the study. Participants (N = 210) were selected from the Fernald Community Cohort based on household water supply from a PFAS-contaminated aquifer. In adjusted repeated measures models, we observed several notable associations between serum PFAS and thyroid hormones as well as kidney function as measured by estimated glomerular filtration rate (eGFR). An interquartile (IQR) increase in serum PFOS was associated with a 0.0975 (95% CI = 1.72, 18.4) increase in thyroid stimulating hormone. An IQR increase in serum PFNA, PFHxS, and PFDeA was associated with a -1.61% (95% CI = -3.53, -0.59), -2.06% (95% CI = -3.53, -0.59), and -2.20% (95% CI = -4.25, -0.14) change in eGFR, respectively. On the other hand, an IQR increase in serum Me-PFOSA was associated with a 0.0153 (95% CI = 0.34, 2.73) increase in eGFR. No significant associations with BMI and serum PFAS were noted. Our findings are in agreement with previous reports that serum PFAS are associated with altered kidney and thyroid function.	●	●								-			B	B
950	ヒト（内分泌系）	Bloom, M. S.; Kannan, K.; Spliethoff, H. M.; Tao, L.; Aldous, K. M.; Vena, J. E.	Exploratory assessment of perfluorinated compounds and human thyroid function	2010	Physiol Behav. 2010 Feb 9;99(2):240-5. doi: 10.1016/j.physbeh.2009.02.005. Epub 2009 Feb 10.	Thyroid hormones play critical roles in human neurodevelopment and adult neurocognitive function. Persistent organohalogen pollutants, such as perfluorinated compounds (PFCs), may interfere with thyroid homeostasis and thus exposures to these compounds might represent risk factors for neurologic and cognitive abnormalities. In this study, serum specimens collected from thirty-one licensed anglers in New York State were analyzed for levels of thyroid stimulating hormone (TSH), free thyroxine (FT(4)), perfluorodecanoic acid (PFDA), perfluorononanoic acid (PFNA), perfluoroheptanoic acid (PFHpA), perfluorohexanesulfonate (PFHxS), perfluorooctanoic acid (PFOA), perfluorooctanesulfonate (PFOS), perfluorooctanesulfonamide (PFOSA), and perfluoroundecanoic acid (PFUnDA). PFOS and PFOA occurred in the highest concentrations with geometric means of 19.6 ng/mL (95% CI 16.3-23.5) and 1.3 ng/mL (95% CI 1.2-1.5), respectively. In a cross-sectional analysis, no statistically significant associations were detected for PFCs, or their sum, with TSH or FT(4) at alpha=0.05. However, post hoc power analyses, though limited, suggested that moderate increases in sample size, to 86 and 129 subjects, might facilitate 0.8 power to detect statistically significant associations for FT(4) and PFDA (beta=0.09) and PFUnDA (beta=0.08), respectively. The consumption of sportfish may have contributed to PFDA (r=0.52, P=0.003) and PFUnDA (r=0.40, P=0.025) levels. This preliminary study does not indicate associations between non-occupational PFCs exposures and thyroid function. However, the possibility for weak associations for FT(4) with PFDA and PFUnDA, PFCs measured in low concentrations, is raised. Given the ubiquity of PFCs in the environment and the importance of thyroid function to neurodevelopmental and neurocognitive endpoints, a confirmatory study is warranted.	●	●	●	●	●					-			C	C
951	ヒト（内分泌系）	Byrne, S. C.; Miller, P.; Seguinot-Medina, S.; Waghiyi, V.; Buck, C. L.; von Hippel, F. A.; Carpenter, D. O.	Exposure to perfluoroalkyl substances and associations with serum thyroid hormones in a remote population of Alaska Natives	2018	Environ Res 166: 537-543. doi: 10.1016/j.envres.2018.06.014. Epub 2018 Jun 27.	Perfluoroalkyl substances (PFASs) are known to accumulate in traditional food animals of the Arctic, and arctic indigenous peoples may be exposed via consumption of subsistence-harvested animals. PFASs are suspected of disrupting thyroid hormone homeostasis in humans. The aim of this study is to assess the relationship between serum PFASs and thyroid function in a remote population of Alaska Natives. Serum samples were collected from 85 individuals from St. Lawrence Island, Alaska. The concentrations of 13 PFASs, as well as free and total thyroxine (T4), free and total triiodothyronine (T3), and thyrotropin (TSH) were quantified in serum samples. The relationships between circulating concentrations of PFASs and thyroid hormones were assessed using multiple linear regression fit with generalized estimating equations. Several PFASs, including perfluorooctanoic acid (PFOA) and perfluorononanoic acid (PFNA), were positively associated with TSH concentrations when modeled individually. PFOS and PFNA were significantly associated with free T3 and PFNA was significantly associated with total T3 in models with PFAS*sex interactive terms; these associations suggested negative associations in men and positive associations in women. PFASs were not significantly associated with concentrations of free or total T4. Serum PFASs are associated with circulating thyroid hormone concentrations in a remote population of Alaska Natives. The effects of PFAS exposure on thyroid hormone homeostasis may differ between sexes.	●	●								-			C	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献クラン①C	文献クラン②B
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
952	ヒト（内分泌系）	Caron-Beaudoin, É.; Ayotte, P.; Laouan Sidi, E. A.; Community of Lac Simon; Community of Winneway – Long Point First Nation; CSSS Tshukuminu Kanani of Nutashkuan; Community of Unamen Shipu; Gros-Louis McHugh, N.; Lemire, M.	Exposure to perfluoroalkyl substances (PFAS) and associations with thyroid parameters in First Nation children and youth from Quebec	2018	Environ Int. 2019 Jul;128:13-23. doi: 10.1016/j.envint.2019.04.029. Epub 2019 Apr 24.	Background: Perfluoroalkyl substances (PFASs) are found in several consumer goods. Exposure to PFASs in children has been associated with alteration in thyroid hormones, which have critical roles in brain function. Objective: In 2015, 198 children and youth (3-19 y) were recruited as part of the pilot project Jeunes, Environnement et Santé/Youth, Environment and Health (JESI-YEH!), realized in collaboration with four First Nation communities in Quebec. We aimed to evaluate serum concentrations of PFASs in relation to concentrations of thyroid-stimulating hormone (TSH), free thyroxine (T4) and thyroglobulin while adjusting for relevant confounders. Methods: PFASs (PFOS, PFOA, PFHxS, PFNA), 2,2',4,4'-Tetrabromodiphenyl ether (PBDE-47) thyroid parameters (TSH, free T4, and thyroglobulin) were measured in serum samples of 186 participants. Iodine, creatinine, and cotinine were measured in urine samples. Serum levels of PFASs were compared to those measured in the general Canadian population and elsewhere. Multivariate regression analyses were performed to determine associations between PFASs and TSH, free T4 and thyroglobulin. Results: PFOS, PFOA and PFHxS serum concentrations were low. However, PFNA concentrations among participants aged 12 to 19 years old from Anishinabe communities were three times higher than those measured in the Canadian Health Measures Survey (2009-2011) for the same age group (Geometric Means: 3.01 µg/L and 0.71 µg/L, respectively) and were particularly higher in the Anishinabe participants aged 6 to 11 years old (GM: 9.44 µg/L). Few participants had levels of TSH, free T4, and thyroglobulin outside age-specific paediatric ranges. When adjusted for relevant covariates and other contaminants, PFNA serum concentrations were positively associated with free T4 levels (Adjusted β = 0.36; p = 0.0014), but not with TSH and thyroglobulin levels. No association was observed between the other PFAS and thyroid hormones parameters. Conclusion: This pilot project reveals among the highest exposure to PFNA in children reported until today, and suggests effects of PFNA as an endocrine disruptor, highlighting the importance of investigating the sources and effects of disproportionate exposure to emerging contaminants in some indigenous communities and ban all PFAS at the international scale.	●	●								-		C	B
953	ヒト（内分泌系）	Caserta, D.; Bordi, G.; Ciardo, F.; Marci, R.; La Rocca, C.; Tait, S.; Bergamasco, B.; Stecca, L.; Mantovani, A.; Guerranti, C.; Fanello, E. L.; Perra, G.; Borghini, F.; Focardi, S. E.; Moscarini, M.	The influence of endocrine disruptors in a selected population of infertile women	2019	Gynecol Endocrinol 29: 444-447. doi: 10.3109/09513590.2012.758702. Epub 2013 Jan 24.	Several studies report that endocrine disrupting chemicals (EDC) able to interfere with endocrine homeostasis may affect women's reproductive health. We analyzed EDC serum levels and nuclear receptors (NRs) expression in order to have an indication of the internal dose of biologically active compounds and a measurement of indicators of their effects, as a result of the repeated uptake from environmental source. The percentage of patients with detectable bisphenol A (BPA) concentrations was significantly higher in the infertile patients compared with fertile subjects. No significant difference was found between the groups with regard to perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), mono-ethylhexyl phthalate (MEHP) and di-(2-ethylhexyl) phthalate (DEHP) concentrations. Among infertile women, the mean expression of estrogen receptor alpha (ERα) and beta (Erβ), androgen receptor (AR) and pregnane X receptor (PXR) was significantly higher than fertile patients. The mean expression of aryl hydrocarbon receptor (AhR) and peroxisome proliferator-activated receptor gamma (PPARγ) did not show significant differences between two groups. Patients with endometriosis had higher levels of PPARγ than all women with other causes of infertility. This study led further support to EDC exposure as a risk factor for women's fertility.	●	●								-		B	C
954	ヒト（内分泌系）	Caserta, D.; Pegoraro, S.; Mallozzi, M.; Di Benedetto, L.; Colicino, E.; Lionetto, L.; Simmaco, M.	Maternal exposure to endocrine disruptors and placental transmission: a pilot study	2018	Gynecol Endocrinol. 2018 Nov;34(11):1001-1004. doi: 10.1080/09513590.2018.1473362. Epub 2018 May 29.	Endocrine disruptors (EDs) are known to affect maternal and child health. The objective of our study was to identify the association between some of the most important endocrine-disruptive substances (perfluorooctane sulfonate [PFOS], perfluorooctanoic acid [PFOA], di2-ethylhexyl-phthalate [DEHP] and mono2-ethylhexyl-phthalate [MEHP]) and both pregnancy variability and birth outcomes. We measured the concentration of the EDs in maternal and cord blood samples of 29 mother-newborn pairs from the Pertini Hospital in Rome between March and June 2016 Each mother reported demographic, life style and diet information. We compared concentrations of the endocrine disruptors between mother and newborn, and among different molecules. We analyzed differences and trends of each ED substance according to the demography and diet information. PFOA levels in maternal blood showed a negative association with newborn weight. Concentration levels of PFOA in both maternal and cord blood of those with physiological progression of pregnancy were higher in than in those with pathological pregnancies. MEHP trend showed a positive association with maternal age. These results confirm the maternal-to-fetus transfer of EDs through the placenta and the impact that endocrine disruptors have on pregnancy and birth outcomes.	●	●								-		C	B
955	ヒト（内分泌系）	Chan, E.; Burstyn, I.; Cherry, N.; Bamforth, F.; Martin, J. W.	Perfluorinated acids and hypothyroxinemia in pregnant women	2011	Environ Res. 2011 May;111(4):559-64. doi: 10.1016/j.envres.2011.01.011. Epub 2011 Feb 9.	Perfluorinated acids (PFAs) are prominent and widespread contaminants of human blood. In animal studies there is evidence that suggests certain PFAs can disrupt thyroid hormone homeostasis. A commonly reported condition in exposed animals is hypothyroxinemia, whereby serum free thyroxine (fT4) is decreased despite normal thyroid stimulating hormone (TSH) concentrations. We designed an individually matched case-control study to investigate whether exposure to perfluorooctanoate (PFOA), perfluorohexane sulfonate (PFHxS), and perfluorooctane sulfonate (PFOS) was associated with hypothyroxinemia in pregnant women from Edmonton, Alberta, Canada, in 2005-2006, who underwent a "triple screen" blood test at 15-20 weeks gestation as part of ante-natal care. Thyroid hormones, fT4 and TSH, were measured in serum from 974 women, and from these we measured PFAs in the sera of 96 hypothyroxinemic cases (normal TSH, the lowest 10th percentile of fT4) and 175 controls (normal TSH, fT4 between the 50th and 90th percentiles) matched on age and referring physician. Analyses by conditional logistic regression indicated that the concentrations of PFAs in this population were not associated with hypothyroxinemia among pregnant women. The current findings do not support a causal link between PFA exposure and maternal hypothyroxinemia in the studied population.	●	●	●	●	●	●				-		C	B
956	ヒト（内分泌系）	Christensen, K. Y.; Raymond, M. R.; Thompson, B. A.; Anderson, H. A.	Fish consumption, levels of nutrients and contaminants, and endocrine-related health outcomes among older male anglers in Wisconsin	2019	J Occup Environ Med 58: 668-675. doi: 10.1097/JOM.0000000000000758.	OBJECTIVE: The aim of this study was to examine associations between endocrine disorders, fish consumption habits, and biomarkers of contaminants and nutrientsMETHODS: : Male anglers aged at least 50 years living in Wisconsin (n = 154) completed a questionnaire and provided biological samples. Adjusted logistic regression models were used to evaluate risk factors for endocrine outcomes.RESULTS: Nineteen percent of anglers reported either pre-diabetes or diabetes, while 0.046 reported thyroid disease. There were few associations between endocrine disease and fish consumption, fish meal source, or species, aside from a notable increase in diabetes risk with lake trout consumption. Docosahexaenoic acid, certain polychlorinated biphenyls (PCBs), and perfluorinated compounds were associated with an increased risk of diabetes or pre-diabetes. PCBs were associated with a decreased risk of thyroid disease.CONCLUSION: Fish consumption patterns may affect risk for endocrine outcomes, but direction and magnitude of association may depend on the balance of the contaminants and nutrients in the individual diet.	●	●								-		C	C
957	ヒト（内分泌系）	Crawford, N. M.; Fenton, S. E.; Strynar, M.; Hines, E. P.; Pritchard, D. A.; Steiner, A. Z.	Effects of perfluorinated chemicals on thyroid function, markers of ovarian reserve, and natural fertility	2017	Reprod Toxicol. 2017 Apr;69:53-59. doi: 10.1016/j.reprotox.2017.01.006. Epub 2017 Jan 19.	Perfluorinated chemicals (PFCs) can act as endocrine-disrupting chemicals, but there has been limited study of their effects on ovarian reserve or fecundability. 99 women, 30-44 years old, without infertility were followed until pregnancy. Initially, serum was evaluated for Antimullerian hormone (AMH), thyroid hormones: thyroid stimulating hormone (TSH), thyroxine (T4), free thyroxine (fT4), and triiodothyronine (T3), and PFCs: perfluorooctanoate (PFOA), perfluorooctane sulfonate (PFOS), perfluorononanoic acid (PFNA), and perfluorohexanesulfonic acid (PFHxS). Bivariate analyses assessed the relationship between thyroid hormones, AMH, and PFCs. Fecundability ratios (FR) were determined for each PFC using a discrete time-varying Cox model and a day-specific probability model. PFC levels were positively correlated with each other (r 0.24-0.90), but there was no correlation with TSH (r 0.02-0.15) or AMH (r -0.01 to -0.15). FR point estimates for each PFC were neither strong nor statistically significant. Although increased exposure to PFCs correlates with thyroid hormone levels, there is no significant association with fecundability or ovarian reserve.	●	●	●	●					●	-		B	B
958	ヒト（内分泌系）	Di Nisio, A.; Sabovic, I.; Valente, U.; Tescari, S.; Rocca, M. S.; Guidolin, D.; Dall'Acqua, S.; Acquasaliente, L.; Pozzi, N.; Plebani, M.; Garolla, A.; Foresta, C.	Endocrine disruption of androgenic activity by perfluoroalkyl substances: clinical and experimental evidence	2019	J Clin Endocrinol Metab 104: 1259-1271. doi: 10.1210/jc.2018-01855.	BACKGROUND: Considerable attention has been paid to perfluoroalkyl compounds (PFCs) because of their worldwide presence in humans, wildlife, and environment. A wide variety of toxicological effects is well supported in animals, including testicular toxicity and male infertility. For these reasons, the understanding of epidemiological associations and of the molecular mechanisms involved in the endocrine-disrupting properties of PFCs on human reproductive health is a major concern.OBJECTIVE: To investigate the relationship between PFC exposure and male reproductive health.DESIGN: This study was performed within a screening protocol to evaluate male reproductive health in high schools.PATIENTS: This is a cross-sectional study on 212 exposed males from the Veneto region, one of the four areas worldwide heavily polluted with PFCs, and 171 nonexposed controls.MAIN OUTCOME MEASURES: Anthropometrics, seminal parameters, and sex hormones were measured in young males from exposed areas compared with age-matched controls. We also performed biochemical studies in established experimental models.RESULTS: We found that increased levels of PFCs in plasma and seminal fluid positively correlate with circulating testosterone (T) and with a reduction of semen quality, testicular volume, penile length, and anogenital distance. Experimental evidence points toward an antagonistic action of perfluorooctanoic acid on the binding of T to androgen receptor (AR) in a gene reporter assay, a competition assay on an AR-coated surface plasmon resonance chip, and an AR nuclear translocation assay.DISCUSSION: This study documents that PFCs have a substantial impact on human health as they interfere with hormonal pathways, potentially leading to male infertility.	●	●	●						●	-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報抽出対象	文献ランク①	文献ランク②
959	ヒト（内分泌系）	Dufour, P.; Pirard, C.; Seghaye, M. C.; Charlier, C.	Association between organohalogenated pollutants in cord blood and thyroid function in newborns and mothers from Belgian population	2018	Environ Pollut. 2018 Jul;238:389-396. doi: 10.1016/j.envpol.2018.03.058. Epub 2018 Mar 26.	The last decades have seen the increasing prevalence of thyroid disorders. These augmentations could be the consequence of the increasing contamination of the environment by chemicals that may disrupt the thyroid function. Indeed, in vitro studies have shown that many chemicals contaminating our environment and highlighted in human serum, are able to interfere with the thyroid function. Given the crucial importance of thyroid hormones on neurodevelopment in fetus and newborns, the influence of these pollutants on newborn thyroid homeostasis is a major health concern. Unfortunately, the overall evidence for a deleterious influence of environmental pollutants on thyroid remains poorly studied. Therefore, we assessed the contamination by polychlorinated biphenyls (PCBs), organochlorine pesticides and perfluorinated compounds (PFC) in 221 cord blood samples collected in Belgium between 2013 and 2016 Our results showed that compared to previous studies performed on newborns recruited in Belgium during the two last decades, the present pollutant contamination is declining. Multivariate statistical analyses pointed out a decrease of thyroid stimulating hormone (TSH) level in male newborns with detectable level of 4,4'- dichlorodiphenyldichloroethylene (4,4'-DDE) in comparison with those with no detectable level (p = 0.025). We also highlighted a negative association between perfluorononanoic acid (PFNA) concentration and TSH in male newborns (p = 0.018). Logistic regression showed increased odds ratio for presentation of hypothyroid in mother for each one unit augmentation of log natural concentration of PFOA (OR = 2.30, [1.18-4.5]) and PFOS (OR = 2.03 [1.08-3.83]). Our findings showed that the residual contamination by PFCs and organochlorine pollutants in cord blood are correlated with thyroid hormone in the newborns and the risk of hypothyroid in mothers.	●	●		●						-	1	B	A
960	ヒト（内分泌系）	Dzierlenga, M. W.; Allen, B. C.; Clewell, H. J.; Longnecker, M. P.	Pharmacokinetic bias analysis of an association between clinical thyroid disease and two perfluoroalkyl substances	2019	Environ Int. 2020 Aug;141:105784. doi: 10.1016/j.envint.2020.105784. Epub 2020 May 11.	Exposure to perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) has been associated with the occurrence of thyroid disease in some epidemiologic studies. We hypothesized that in a specific epidemiologic study based on the National Health and Nutrition Examination Survey, the association of clinical thyroid disease with serum concentration of PFOA and PFOS was due to reverse causality. Thyroid hormone affects glomerular filtration, which in turn affects excretion of PFOA and PFOS. We evaluated this by linking a model of thyroid disease status over the lifetime to a physiologically based pharmacokinetic model of PFOA and PFOS. Using Monte Carlo methods, we simulated the target study population and analyzed the data using multivariable logistic regression. The target and simulated populations were similar with respect to age, estimated glomerular filtration rate, serum concentrations of PFOA and PFOS, and prevalence of clinical thyroid disease. The analysis showed little or no evidence of bias from the hypothesized mechanism. The largest bias was for the fourth quartile of PFOA in females, with an odds ratio of 0.93 (95% CI, 0.90, 0.97). The reported odds ratio of clinical thyroid disease for this group was 1.63 (1.07, 2.47), and if it were corrected for the bias would have been 1.74 (1.14, 2.65). Our results suggest that little of the reported association in the target study was due to reverse causality.	●	●								-	1	A	A
961	ヒト（内分泌系）	Dzierlenga, M. W.; Allen, B. C.; Ward, P. L.; Clewell, H. J.; Longnecker, M. P.	A model of functional thyroid disease status over the lifetime	2020	PLoS ONE. 2019 Jul 18;14(7):e0219769. doi: 10.1371/journal.pone.0219769. eCollection 2019.	Mathematical models of the natural history of disease can predict incidence rates based on prevalence data and support simulations of populations where thyroid function affects other aspects of physiology. We developed a Markov chain model of functional thyroid disease status over the lifetime. Subjects were in one of seven thyroid disease states at any given point in their lives [normal, subclinical hypothyroidism, overt hypothyroidism, treated thyroid disease (ever), subclinical hyperthyroidism, overt hyperthyroidism, and reverted to normal thyroid status]. We used a Bayesian approach to fitting model parameters. A priori probabilities of changing from each disease state to another per unit time were based on published data and summarized using meta-analysis, when possible. The probabilities of changing state were fitted to observed prevalence data based on the National Health and Nutrition Examination Survey 2007-2012. The fitted model provided a satisfactory fit to the observed prevalence data for each disease state, by sex and decade of age. For example, for males 50-59 years old, the observed prevalence of ever having treated thyroid disease was 0.044 and the predicted value was 4.6%. Comparing the incidence rates of treated disease predicted from our model with published values revealed that 0.82 were within a 4-fold difference. The differences seemed to be systematic and were consistent with expectation based on national iodine intakes. The model provided new and comprehensive estimates of functional thyroid disease incidence rates for the U.S. Because the model provides a reasonable fit to national prevalence data and predicts thyroid disease status over the lifetime, it is suitable for simulating populations, thereby making possible quantitative bias analyses of selected epidemiologic data reporting an association of thyroid disease with serum concentrations of environmental contaminants.	●	●								-		C	C
962	ヒト（内分泌系）	Dzierlenga, M. W.; Moreau, M.; Song, G.; Mallick, P.; Ward, P. L.; Campbell, J. L.; Housand, C.; Yoon, M.; Allen, B. C.; Clewell, H. J.; Longnecker, M. P.	Quantitative bias analysis of the association between subclinical thyroid disease and two perfluoroalkyl substances in a single study	2020	Environ Res. 2020 Mar;182:109017. doi: 10.1016/j.envres.2019.109017. Epub 2019 Dec 9.	Exposure to perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) has been associated with the occurrence of thyroid disease in some epidemiologic studies. We hypothesized that in a specific epidemiologic study based on the National Health and Nutrition Examination Survey, the association of subclinical thyroid disease with serum concentration of PFOA and PFOS was due to reverse causality. Thyroid hormone affects glomerular filtration, which in turn affects excretion of PFOA and PFOS. We evaluated this by linking a model of thyroid disease status over the lifetime to physiologically based pharmacokinetic models of PFOA and PFOS. Using Monte Carlo methods, we simulated the target study population and analyzed the data using multivariable logistic regression. The target and simulated populations were similar with respect to age, estimated glomerular filtration rate, serum concentrations of PFOA and PFOS, and prevalence of subclinical thyroid disease. Our findings suggest that in the target study the associations with subclinical hypothyroidism were overstated and the results for subclinical hyperthyroidism were, in general, understated. For example, for subclinical hypothyroidism in men, the reported odds ratio per ln(PFOS) increase was 1.98 (95% CI 1.19-3.28), whereas in the simulated data the bias due to reverse causality gave an odds ratio of 1.19 (1.16-1.23). Our results provide evidence of bias due to reverse causality in a specific cross-sectional study of subclinical thyroid disease with exposure to PFOA and PFOS among adults.	●	●								-	1	A	A
963	ヒト（内分泌系）	Ernst, A.; Brix, N.; Lauridsen, L. L. B.; Olsen, J.; Parner, E. T.; Liew, Z.; Olsen, L. H.; Ramlau-Hansen, C. H.	Exposure to perfluoroalkyl substances during fetal life and pubertal development in boys and girls from the danish national birth cohort	2019	Environ Health Perspect. 2019 Jan;127(1):17004. doi: 10.1289/EHP3567.	BACKGROUND: It remains unsettled whether prenatal exposure to perfluoroalkyl substances (PFASs) affects human reproductive health through potential endocrine disruption.OBJECTIVES: We aimed to explore the associations between prenatal exposure to several PFASs and various aspects of pubertal development in boys and girls.METHODS: We studied two samples ([Formula: see text] and 445) from the Puberty Cohort, nested within the Danish National Birth Cohort (DNBC), measuring PFAS in maternal plasma from early gestation. Data on pubertal development were collected biannually from the age of 11 y until full maturation, using web-based questionnaires. Outcomes were age at menarche, voice break, first ejaculation, and Tanner stages 2 to 5 for pubic hair, breast, genital development, and a combined puberty indicator. A regression model for censored data was used to estimate mean difference (months) in age at achieving the pubertal outcomes across tertiles of PFAS concentrations and with a doubling of PFAS concentrations (continuous). For perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS), a meta-analysis was used to provide a weighted average of the point estimates from samples 1 and 2.RESULTS: Overall, prenatal exposure to PFOS, perfluorohexane sulfonate (PFHxS), perfluoroheptane sulfonate (PFHpS), perfluorononanoic acid (PFNA), and perfluorodecanoic acid (PDFA) (girls) and PFHxS and PFHpS (boys) was associated with lower mean age at puberty marker onset. PFDA and PFNA exposure was associated with higher mean age at onset of puberty in boys. Nonmonotonic associations in girls (PFOS, PFHpS, PFDA) and boys (PFDA, PFNA) were observed, showing larger mean age differences for the combined puberty indicator in the middle tertile [girls: PFOS: [Formula: see text] mo, 0.95 confidence interval (CI): [Formula: see text], [Formula: see text]; PFHpS: [Formula: see text] mo, 0.95 CI: [Formula: see text], 1.85; PFDA: [Formula: see text] mo, 0.95 CI: [Formula: see text], 1.83; and boys: PFNA: 4.45 mo, 0.95 CI: [Formula: see text], 10.21; PFDA: 4.59 mo, 0.95 CI: [Formula: see text], 10.11] than in the highest tertile with the lowest as reference.CONCLUSIONS: Our population-based cohort study suggests sex-specific associations of altered pubertal development with prenatal exposure to PFASs. These findings are novel, and replication is needed.	●	●	●							-	1	A	A
964	ヒト（内分泌系）	Heffernan, A. L.; Cunningham, T. K.; Drage, D. S.; Aylward, L. L.; Thompson, K.; Vijayasarathy, S.; Mueller, J. F.; Atkin, S. L.; Sathyapalan, T.	Perfluorinated alkyl acids in the serum and follicular fluid of UK women with and without polycystic ovarian syndrome undergoing fertility treatment and associations with hormonal and metabolic parameters	2019	Int J Hyg Environ Health 221: 1068-1075. doi: 10.1016/j.ijheh.2018.07.009. Epub 2018 Jul 20.	Women with polycystic ovarian syndrome (PCOS) undergoing treatment for infertility could be a sensitive subpopulation for endocrine effects of exposure to perfluorinated alkyl acids (PFAAs), persistent organic pollutants with potential endocrine activity. Women with, PCOS (n = 30) and age- and BMI-matched controls (n = 29) were recruited from a UK fertility clinic in 2015 Paired serum and follicular fluid samples were collected and analysed for 13 PFAAs. Sex steroid and thyroid hormones, and metabolic markers were measured and assessed for associations with serum PFAAs. Four PFAAs were detected in all serum and follicular fluid samples and concentrations in the two matrices were highly correlated ($R^2 > 0.95$): perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), perfluorohexane sulfonate (PFHxS), and perfluorononanoic acid (PFNA). Serum PFOS was positively associated with age (1 ng/mL per yr, $p < 0.05$) and was higher in PCOS cases than controls (geometric mean [GM] 3.9 vs. 3.1 ng/mL, $p < 0.05$) and in women with irregular vs. regular menstrual cycles (GM 3.9 vs. 3.0 ng/mL, p = 0.01). After adjustment for confounders, serum testosterone was significantly associated with PFOA, PFHxS, PFNA, and the molar sum of the four frequently detected serum PFAAs (approximately 50 percent increase per ln-unit) among controls but not PCOS cases. HbA1c in PCOS cases was inversely associated with serum PFOA, PFHxs, and sum of PFAAs (2-3 mmol/mol per ln-unit). In controls, fasting glucose was positively associated with serum PFOA and sum of PFAAs (0.25 nmol/L per ln-unit increase in PFAAs). Few other associations were observed. The analyses and findings here should be considered exploratory in light of the relatively small sample sizes and large number of statistical comparisons conducted. However, the data do not suggest increased sensitivity to potential endocrine effects of PFAAs in PCOS patients.	●	●	●							-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ランク①	文献ランク②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
965	ヒト（内分泌系）	Inoue, K.; Ritz, B.; Andersen, S. L.; Ramlau-Hansen, C. H.; Høyer, B. B.; Bech, B. H.; Henriksen, T. B.; Bonefeld-Jørgensen, E. C.; Olsen, J.; Liew, Z.	Perfluoroalkyl Substances and Maternal Thyroid Hormones in Early Pregnancy; Findings in the Danish National Birth Cohort	2019	Environ Health Perspect. 2019 Nov;127(11):117002. doi: 10.1289/EHP5482. Epub 2019 Nov 12.	BACKGROUND: Maternal thyroid hormones are essential for fetal brain development in early gestation. Perfluoroalkyl substances (PFASs)-widespread and persistent pollutants-have been suggested to interfere with maternal thyroid hormones in the second or third trimesters, but evidence for an association in the early pregnancy period is sparse.OBJECTIVES: Our goal was to evaluate the gestational-week specific associations of maternal thyroid-stimulating hormone (TSH) and free thyroxine (fT4) levels with plasma concentrations of six PFAS chemicals in the first and second pregnancy trimester.METHODS: A cross-sectional analysis was conducted using 1366 maternal blood samples collected between gestational weeks (GWs) 5 and 19 (median, 8 gestational weeks) in the Danish National Birth Cohort (DNBC) during 1996-2002. We estimated the percentage changes of serum TSH and fT4 levels according to concentrations (in nanograms per milliliter) of six PFAS chemicals modeled as per interquartile range (IQR) increase or by exposure quartiles. Moreover, we contrasted the estimated week-specific TSH or fT4 levels by PFAS quartile and estimated ORs for binary high or low TSH and fT4 status based on the week-specific distribution according to IQR increase of PFAS.RESULTS: TSH levels followed a U-curve trend in early pregnancy with a nadir at GW10, whereas fT4 levels were less fluctuated in the samples. There were no apparent associations between any of the PFASs and changes of average TSH or fT4 levels in total samples. In gestational-week-specific analyses, we found that the estimated TSH values were higher among the highest perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), perfluorohexane sulfonate (PFHxS), and perfluoroheptane sulfonate (PFHpS) quartiles compared with the lower quartiles from GW5 to GW10, but the difference became null or even reversed after GW10. For binary outcomes, perfluorodecanoic acid (PFDA) was associated with high fT4 status before GW10 [(95% CI: 1.04, 2.05)].CONCLUSIONS: We observed some gestational-week-specific associations between high exposure to several PFAS and TSH level in early gestations. Further research of the biology and the potential clinical impact regarding thyroid hormones disruptions in early pregnancy is needed.	●	●							●	-		B	B
966	ヒト（内分泌系）	Itoh, S.; Araki, A.; Miyashita, C.; Yamazaki, K.; Goudarzi, H.; Minatoya, M.; Ait Bamai, Y.; Kobayashi, S.; Okada, E.; Kashino, I.; Yuasa, M.; Baba, T.; Kishi, R.	Association between perfluoroalkyl substance exposure and thyroid hormone/thyroid antibody levels in maternal and cord blood: The Hokkaido Study	2019	Environ Int. 2019 Dec;133(Pt A):105139. doi: 10.1016/j.envint.2019.105139. Epub 2019 Sep 10.	BACKGROUND: Thyroid antibodies (TAs) are the most common cause of hypothyroidism during gestation. Although previous studies found that prenatal exposure to perfluoroalkyl substances (PFASs) disrupts thyroid hormones (THs) in humans, their effects on TAs during the perinatal period have not been investigated.OBJECTIVE: To explore the associations between prenatal exposure to eleven different PFASs from two different groups (carboxylates and sulfonates) and the expression of THs and TAs in maternal and cord blood while considering maternal TA status.METHODS: In a prospective birth cohort (the Hokkaido Study), we included 701 mother–neonate pairs recruited in 2002-2005 for whom both prenatal maternal and cord blood samples were available. Eleven PFASs were measured in maternal plasma obtained at 28-32 weeks of gestation using ultra-performance liquid chromatography coupled with triple quadrupole tandem mass spectrometry. THs and TAs including thyroid stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), thyroid peroxidase antibody (TPOAb), and thyroglobulin antibody (TgAb) were measured in maternal blood during early pregnancy (median 11 gestational weeks), and in cord blood at birth.RESULTS: The median levels of TgAb and TPOAb in maternal serum were 15 and 6.0 IU/mL, respectively. The median TgAb level in neonates was 38.0 IU/mL, and TPOAb were detected in only 0.123 of samples. Maternal FT3 level was positively associated with PFAS levels in both TA-positive and TA-negative mothers. Maternal perfluorooctanoate was inversely associated with maternal TPOAb. Among boys, some maternal PFASs were associated with higher TSH and lower FT3 levels in maternal TA-negative group, while perfluorodecanoic acid was associated with lower TSH in maternal TA-positive group. Among girls, some PFAS of mothers showed associations with lower TSH and higher FT3 in maternal TA-negative group, while perfluorododecanoic acid was associated with lower FT4 in maternal TA-positive. Maternal PFASs showed associations with boy's TgAb inversely in maternal TA-negative group and with girl's TgAb positively in maternal TA-positive group.CONCLUSIONS: Our results suggest thyroid disrupting effects of PFAS exposure and susceptibility vary depending on maternal TA levels.	●	●								-	1	B	A
967	ヒト（内分泌系）	Jain, R.	Association between thyroid profile and perfluoroalkyl acids: Data from NHNAES 2007-2008	2013	Environ Res. 2013 Oct;126:51-9. doi: 10.1016/j.envres.2013.08.006. Epub 2013 Sep 18.	The effect of six perfluoroalkyl acids (PFAAs), namely, perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), perfluorodecanoic acid (PFDE), perfluorohexane sulfonic acid (PFHxS), 2-(N-methylperfluorooctane sulfonamide) acetic acid (MPAH), and perfluorononanoic acid (PFNA) on the levels of six thyroid function variables, namely, thyroid stimulating hormone (TSH), free and total thyroxine (FT4, TT4), free and total triiodothyronine (FT3, TT3), and thyroglobulin (TGN) was evaluated. Data from National Health and Nutrition Examination Survey for the years 2007-2008 were used for this evaluation. TSH levels increased with increase in levels of PFOA ($p < 0.01$). There were no statistically significant associations between the levels of FT3, and FT4 with the levels of any of the six PFAAs. Levels of TT3 were found to increase with the levels of PFOA ($p = 0.01$) and TT4 levels were found to increase with increase in PFHxS levels ($p < 0.01$). Males had statistically significantly higher levels of FT3 than females and females had statistically significantly higher levels of TT4 than males. As compared to non-Hispanics whites and Hispanics, non-Hispanic blacks had lower levels of TSH, FT3, TT3, and TT4 but Hispanics had the lowest levels of TGN. Age was negatively associated with FT3 and TT3 but positively associated with FT4 and TT4. Non-smokers had higher levels of TSH and TT4 than smokers and smokers had higher levels of FT3 and TGN than non-smokers. Iodine deficiency was associated with increased levels of TSH, TT3, TT4, and TGN. (C) 2013 Elsevier Inc. All rights reserved.	●	●	●	●						-		B	B
968	ヒト（内分泌系）	Jain, R. B.; Ducatman, A.	Perfluoroalkyl acids and thyroid hormones across stages of kidney function	2019	Sci Total Environ. 2019 Dec 15;696:133994. doi: 10.1016/j.scitotenv.2019.133994. Epub 2019 Aug 19.	Data for US adults aged ≥20 years for 2007-2012 (N = 7020) were used to study concentrations of thyroid stimulating hormone (TSH), free (FT3) and total triiodothyronine (TT3), free (FT4) total thyroxine (TT4), and thyroglobulin (TGN) across stages of glomerular function (GF). Data for 2007-2008 and 2011-2012 (N = 2549) were used to study associations between thyroid hormone biomarkers and five serum perfluoroalkyl acids (PFAAs). We report how thyroid hormone biomarkers vary in human serum across stages of GF. Stages considered were: GF-1 (normal, eGFR >90 mL/min/1.73 m2), GF-2 (60 ≤ eGFR≤90 mL/min/1.73 m2), GF-3A (45 ≤ eGFR<60 mL/min/1.73 m2), and GF-3B/4 (15 ≤ eGFR<45 mL/min/1.73 m2). Regression models stratified by GF stages were fitted to evaluate associations between the concentrations of selected PFAAs and thyroid hormones and to evaluate the variability in concentrations of thyroid hormones across the stages of GF. Adjusted geometric means (AGM) for TSH sharply increased from GF-1 (1.34 μIU/mL) to GF-2 (1.58 μIU/mL) and then remained relatively stable. AGMs of FT3 and TT3 decreased consistently from GF-1 to GF-3B/4; from 3.24 to 2.79 pg/mL for FT3 and from 115.7 to 96.4 ng/dL for TT3. AGMs for FT4 increased from GF-2 onward. TGN increased as glomerular filtration worsened from GF-1 through GF-3B/4. In contrast to strong relationships of thyroid hormone markers to stages of renal function, only scattered, inconsistent findings characterized relationship of PFAAs to thyroid markers across stages of kidney disease. For example, TSH was positively associated with PFOA at GF-2 ($\beta = 0.08522$, $p < 0.01$) but negatively associated at GF-3A ($\beta = -0.22926$, $p = 0.04$). Thus, associations between kidney disease and thyroid hormone are clear, but the relationships between PFAAs and thyroid hormones vary inconsistently from stage to stage and reveal no trend. For thyroid hormone investigations, we conclude stratification by glomerular function stage is likely not needed.	●	●								-		B	C
969	ヒト（内分泌系）	Joensen, Ulla Nordström; Veyrand, Bruno; Antignac, Jean-Philippe; Blomberg Jensen, Martin; Petersen, Jørgen Holm; Marchand, Philippe; Skakkebæk, Niels Erik; Andersson, Anna-Maria; Le Bizec, Bruno; Jørgensen, Niels	PFOS (perfluorooctanesulfonate) in serum is negatively associated with testosterone levels, but not with semen quality, in healthy men	2013	Hum Reprod. 2013 Mar;28(3):599-608. doi: 10.1093/humrep/des425. Epub 2012 Dec 18.	STUDY QUESTION: Is exposure to perfluorinated compounds (PFCs) associated with testicular function (reproductive hormone levels and semen quality) in healthy men? SUMMARY ANSWER: PFOS levels were significantly negatively associated with serum testosterone (total and calculated free), but not with any other reproductive hormones or semen quality. WHAT IS KNOWN ALREADY: In animals, some PFCs have endocrine disrupting potential, but few studies have investigated PFCs in relation to human testicular function. Previously, we and others have observed a negative association between serum PFC levels and sperm morphology. The potential associations with reproductive hormones remain largely unresolved. STUDY DESIGN, SIZE, DURATION: A cross-sectional study of 247 men was conducted during 2008-2009. PARTICIPANTS/MATERIALS, SETTING, METHODS: Healthy men from the general population, median age of 19 years, gave serum and semen samples. Serum samples were analysed for total testosterone (T), estradiol (E), sex hormone-binding globulin (SHBG), luteinizing hormone (LH), follicle-stimulating hormone (FSH) and inhibin-B and 14 PFCs, including perfluorooctanesulfonate (PFOS). Semen samples were analysed according to the WHO criteria. MAIN RESULTS AND THE ROLE OF CHANCE: PFOS levels were negatively associated with testosterone (T), calculated free testosterone (FT), free androgen index (FAI) and ratios of T/LH, FAI/LH and FT/LH. Other PFCs were found at lower levels than PFOS and did not exhibit the same associations. PFC levels were not significantly associated with semen quality. PFOS levels in these samples collected in 2008-2009 were lower than in our previous study of men participating in 2003. LIMITATIONS, REASONS FOR CAUTION: Results were robust to adjustment for relevant confounders; however, the possibility of chance associations due to multiple testing or effects of uncontrolled confounding cannot be ruled out. WIDER IMPLICATIONS OF THE FINDINGS: Our previous findings of decreased sperm morphology in the most highly PFC exposed men were not replicated, possibly due to a lack of highly exposed individuals; however, a recent independent study also did corroborate such an inverse association. The negative association between serum PFOS and testosterone indicates that testosterone production may be compromised in individuals with high PFOS exposure. STUDY FUNDING/COMPETING INTEREST(S): The authors received financial support from the European Commission (DEER, FP7-2007-212844), the Danish Agency for Science, Technology and Innovation (grant nos. 27107068 and 09-067180), Rigshospitalet (grant no. 961506336), the University of Copenhagen, the Danish Ministry of Health and the Danish Environmental Protection Agency (MST-621-00013), and Kirsten and Freddy Johansen Foundation (grant no. 95-103-72087). The funding organizations played no role in the design and conduct of the study, in collection, management, analysis and interpretation of the data; or in the presentation, review or approval of the manuscript. The authors declare that they have no competing financial interests.	●	●	●	●					●	-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
970	ヒト（内分泌系）	Kato, S.; Itoh, S.; Yuasa, M.; Baba, T.; Miyashita, C.; Sasaki, S.; Nakajima, S.; Uno, A.; Nakazawa, H.; Iwasaki, Y.; Okada, E.; Kishi, R.	Association of perfluorinated chemical exposure in utero with maternal and infant thyroid hormone levels in the Sapporo cohort of Hokkaido Study on the Environment and Children's Health	2016	Environ Health Prev Med. 2016 Sep;21(5):334-344. doi: 10.1007/s12199-016-0534-2. Epub 2016 Apr 30.	OBJECTIVES: Perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) have been widely used as industrial products, and are persistent organic pollutants due to their chemical stability. Previous studies suggested that PFOS and PFOA might disrupt thyroid hormone (TH) status. Although TH plays an important role in fetal growth during pregnancy, little attention has been paid to the relationships between maternal exposure to perfluorocarbons and TH statuses of mothers and fetuses. We investigated the effects of low levels of environmental PFOS and PFOA on thyroid function of mothers and infants.METHODS: Of the eligible subjects in a prospective cohort, 392 mother-infant pairs were selected. Concentration of maternal serum PFOS and PFOA was measured in samples taken during the second and third trimesters or within 1 week of delivery. Blood samples for measuring thyroid stimulating hormone (TSH) and free thyroxine (FT4) levels were obtained from mothers at early gestational stage (median 11.1 weeks), and from infants between 4 and 7 days of age, respectively.RESULTS: Median concentrations of PFOS and PFOA were 5.2 [95 % confidence interval (CI) 1.6-12.3] and 1.2 (95 % CI limitation of detection-3.4) ng/mL, respectively. Maternal PFOS levels were inversely correlated with maternal serum TSH and positively associated with infant serum TSH, whereas maternal PFOA showed no significant relationship with TSH or FT4 among mothers and infants.CONCLUSIONS: These findings suggest that PFOS may independently affect the secretion and balances of maternal and infant TSH even at low levels of environmental exposure.	●	●							-	1	A	B
971	ヒト（内分泌系）	Kim, D. H.; Kim, U. J.; Kim, H. Y.; Choi, S. D.; Oh, J. E.	Perfluoroalkyl substances in serum from South Korean infants with congenital hypothyroidism and healthy infants - Its relationship with thyroid hormones	2016	Environ Res. 2016 May;147:399-404. doi: 10.1016/j.envres.2016.02.037. Epub 2016 Mar 4.	Exposure to perfluoroalkyl substances (PFASs) may disrupt thyroid systems, though the specific effects of PFASs are still being elucidated. Since research regarding exposure in infants is highly limited, our goal was to investigate exposure levels of PFASs in infant serum and correlate these levels with thyroid hormones (THs). This was accomplished by analyzing 16 PFASs in sera from a case group of infants with congenital hypothyroidism and a control group. Total PFAS exposure level was 2.63-44.7ng/mL in the case group and 2.44-22.4ng/mL in the control group. Concentrations of serum perfluorooctanoic acid (PFOA, p<0.01), perfluorononanoic acid (PFNA, p<0.001), perfluorooctanoic acid (PFDA, p<0.005), and perfluoroundecanoic acid (PFUnDA, p<0.005) were significantly higher in the case group than the control group. Levels of certain PFASs (PFOA, perfluorotridecanoic acid [PFTrDA], and perfluorohexane sulfonate [PFHxS]) showed a moderate to weak correlation with relevant antibodies.	●	●	●	●					-		B	B
972	ヒト（内分泌系）	Kim, H. Y.; Kim, K. N.; Shin, C. H.; Lim, Y. H.; Kim, J. I.; Kim, B. N.; Hong, Y. C.; Lee, Y. A.	Per- and poly-fluoroalkyl substances (PFASs) in follicular fluid from women experiencing infertility in Australia	2020	Environ Res. 2020 Nov;190:109963. doi: 10.1016/j.envres.2020.109963. Epub 2020 Jul 21.	Background: Exposure to perfluoroalkyl substances (PFAS) has been suggested to affect thyroid function; however, data on early-life exposure and thyroid function in early childhood are scarce. We investigated the cross-sectional and longitudinal relationships of early-life exposure to PFAS with thyroid function at 2, 4, and 6 years of age.	●	●							-		D	C
973	ヒト（内分泌系）	Knox, S. S.; Jackson, T.; Javins, B.; Frisbee, S. J.; Shankar, A.; Ducatman, A. M.	Implications of early menopause in women exposed to perfluorocarbons	2011	J Clin Endocrinol Metab. 2011 Jun;96(6):1747-53. doi: 10.1210/jc.2010-2401. Epub 2011 Mar 16.	CONTEXT: Perfluorocarbons (PFC) are man-made chemicals used in numerous household products. They have a long half-life in humans and complex animal toxicity, and accumulating evidence points toward associations with multiple human health endpoints.OBJECTIVE: Our objective was to investigate whether PFC are associated with endocrine disruption in women.DESIGN: Cross-sectional analyses were made between quintiles of serum PFC, serum estradiol, and menopause onset.SETTING: The C8 Health Project, with cohort of 69030 adults and children, was conducted due to PFC contamination of drinking water from six water districts in two states.PARTICIPANTS: Participants included 25957 women aged 18-65 yr.MAIN OUTCOME MEASURES: Serum estradiol levels and onset of menopause were assessed. The survey was the result of a class action suit, and survey designers (an independent corporation) had no a priori hypotheses. All hypotheses have been formulated by other investigators after data collection.RESULTS: After excluding women who reported hysterectomy and adjusting for age within the group, smoking, alcohol consumption, body mass index, and exercise, the odds of having experienced menopause were significantly higher in the highest quintile relative to the lowest quintile of perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) in the perimenopausal [PFOS odds = 1.4, confidence interval (CI) = 1.1-1.8; PFOA odds =1.4, CI = 1.1-1.8] and menopausal age groups (PFOS odds = 2.1, CI=1.6-2.8; PFOA odds = 1.7, CI = 1.3-2.3). After appropriate exclusions and adjustment for covariates, there was a significant inverse association between PFOS and estradiol in perimenopausal (β = -3.65; P < 0.0001) and menopausal age groups (β = -0.83; P = 0.007) but not between PFOA and estradiol.CONCLUSIONS: These data suggest that PFC are associated with endocrine disruption in women and that further research on mechanisms is warranted.	●	●		●	●	●			-		B	B
974	ヒト（内分泌系）	Lebeaux, R. M.; Doherty, B. T.; Gallagher, L. G.; Zoeller, R. T.; Hoofnagle, A. N.; Calafat, A. M.; Karagas, M. R.; Yolton, K.; Chen, A.; Lanphear, B. P.; Braun, J. M.; Romano, M. E.	Maternal serum perfluoroalkyl substance mixtures and thyroid hormone concentrations in maternal and cord sera: The HOME Study	2020	Environ Res. 2020 Jun;185:109395. doi: 10.1016/j.envres.2020.109395. Epub 2020 Mar 16.	BACKGROUND: Per- and polyfluoroalkyl substances (PFAS) are ubiquitous. Previous studies have found associations between PFAS and thyroid hormones in maternal and cord sera, but the results are inconsistent. To further address this research question, we used mixture modeling to assess the associations with individual PFAS, interactions among PFAS chemicals, and the overall mixture.METHODS: We collected data through the Health Outcomes and Measures of the Environment (HOME) Study, a prospective cohort study that between 2003 and 2006 enrolled 468 pregnant women and their children in the greater Cincinnati, Ohio region. We assessed the associations of maternal serum PFAS concentrations measured during pregnancy with maternal (n = 185) and cord (n = 256) sera thyroid stimulating hormone (TSH), total thyroxine (TT4), total triiodothyronine (TT3), free thyroxine (FT4), and free triiodothyronine (FT3) using two mixture modeling approaches (Bayesian kernel machine regression (BKMR) and quantile g-computation) and multivariable linear regression. Additional models considered thyroid autoantibodies, other non-PFAS chemicals, and iodine deficiency as potential confounders or effect measure modifiers.RESULTS: PFAS, considered individually or as mixtures, were generally not associated with any thyroid hormones. A doubling of perfluorooctanesulfonic acid (PFOS) had a positive association with cord serum TSH in BKMR models but the 0.95 Credible Interval included the null (β = 0.09; 0.95 CrI: -0.08, 0.27). Using BKMR and multivariable models, we found that among children born to mothers with higher thyroid peroxidase antibody (TPOAb), perfluorooctanoic acid (PFOA), PFOS, and perfluorohexanesulfonic acid (PFHxS) were associated with decreased cord FT4 suggesting modification by maternal TPOAb status.CONCLUSIONS: These findings suggest that maternal serum PFAS concentrations measured in the second trimester of pregnancy are not strongly associated with thyroid hormones in maternal and cord sera. Further analyses using robust mixture models in other cohorts are required to corroborate these findings.	●	●							-		B	B
975	ヒト（内分泌系）	Li, Y.; Cheng, Y.; Xie, Z.; Zeng, F.	Perfluorinated alkyl substances in serum of the southern Chinese general population and potential impact on thyroid hormones	2017	Sci Rep. 2017 Feb 27;7:43380. doi: 10.1038/srep43380.	In this study, eight perfluorinated alkyl substances (PFASs) and five thyroid hormones (TSH, FT4, FT3, TGAb, and TMAb) were determined in 202 human serum samples of the general population of Guangdong, Guangxi and Hainan provinces in southern China. Σ8PFASs concentrations ranged from 0.85 to 24.3 ng/mL with a mean value of 4.66 ng/mL. The PFASs composition profiles of human serum samples nearly make no difference at different locations. A significant increase was observed for Σ8PFASs, PFOS, and PFHxS concentrations with age ($p < 0.01$). Gender-related differences were found; PFOS, PFHxS, PFBS, and PFOA levels were higher in males ($p < 0.05$), and the mean concentration of Σ8PFASs was 1.5 times greater in males (6.02 ng/mL) than in females (4.15 ng/mL). PFOS and Σ8PFASs were significantly negatively correlated with FT3 and FT4 and positively correlated with TSH while PFPeA and PFHxA were significantly positively correlated with TGAb and TMAb in all the samples. The opposite associations between FT3, TSH and PFOS, PFOA and PFHxS levels in hypothyroidism and hyperthyroidism group indicate that the PFOS, PFOA and PFHxS enhance the negative feedback mechanisms of the thyroid gland.	●	●	●						-		B	C
976	ヒト（内分泌系）	Lin, Chien-Yu; Wen, Li-Li; Lin, Lian-Yu; Wen, Ting-Wen; Lien, Guang-Wen; Hsu, Sandy H J; Chien, Kuo-Liong; Liao, Chien-Chang; Sung, Fung-Chang; Chen, Pau-Chung; Su, Ta-Chen	The associations between serum perfluorinated chemicals and thyroid function in adolescents and young adults	2013	J Hazard Mater. 2013 Jan 15;244-245:637-44. doi: 10.1016/j.jhazmat.2012.10.049. Epub 2012 Nov 2.	Perfluorinated chemicals (PFCs) have been widely used in a variety of products worldwide for years. However, the effect of PFCs on thyroid function has not yet been clearly defined. We recruited 567 subjects (aged 12-30 years) in a population-based cohort of adolescents and young adults with abnormal urinalysis in the childhood to determine the relationship between serum level of PFCs and the levels of serum free thyroxine (T4) and thyroid stimulating hormone (TSH). The geometric means and geometric standard deviation concentrations of perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), perfluorononanoic acid (PFNA) and perfluoroundecanoic acid (PFUA) were 2.67 (2.96) ng/ml, 7.78 (2.42) ng/ml, 1.01 (3.48) ng/ml and 5.81 (2.92) ng/ml, respectively. Differences in the levels of free T4 and TSH across different categories of PFOA, PFOS and PFUA were insignificant. After controlling for confounding factors, multiple linear regression analyses revealed mean serum level of free T4 increased significantly across categories (<60th, 60-89 and >90th percentiles) of PFNA (P for trend =0.012 in the full model). The association between PFNA and free T4 was more significant in male subjects in age group 20-30, active smokers and in those with higher body mass index in stratified analysis. Serum concentrations of PFNA were associated with serum free T4 levels in adolescents and young adults.	●	●	●						-		B	B
977	ヒト（内分泌系）	Lopez-Espinosa, M. J.; Mondal, D.; Armstrong, B.; Bloom, M. S.; Fletcher, T.	Thyroid function and perfluoroalkyl acids in children living near a chemical plant	2012	Environ Health Perspect. 2012 Jul;120(7):1036-41. doi: 10.1289/ehp.1104370. Epub 2012 Mar 27.	BACKGROUND: Animal studies suggest that some perfluoroalkyl acids (PFAAs), including perfluorooctanoate (PFOA), perfluorooctane sulfonate (PFOS), and perfluorononanoic acid (PFNA) may impair thyroid function. Epidemiological findings, mostly related to adults, are inconsistent.OBJECTIVES: We investigated whether concentrations of PFAAs were associated with thyroid function among 10725 children (1-17 years of age) living near a Teflon manufacturing facility in the Mid-Ohio Valley (USA).METHODS: Serum levels of thyroid-stimulating hormone (TSH), total thyroxine (TT4), and PFAAs were measured during 2005-2006, and information on diagnosed thyroid disease was collected by questionnaire. Modeled in utero PFOA concentrations were based on historical information on PFOA releases, environmental distribution, pharmacokinetic modeling, and residential histories. We performed multivariate regression analyses.RESULTS: Median concentrations of modeled in utero PFOA and measured serum PFOA, PFOS, and PFNA were 12, 29, 20, and 1.5 ng/mL, respectively. The odds ratio for hypothyroidism (n = 39) was 1.54 [95% confidence interval (CI): 1.00, 2.37] for an interquartile range (IQR) contrast of 13 to 68 ng/mL in serum PFOA measured in 2005-2006. However, an IQR shift in serum PFOA was not associated with TSH or TT4 levels in all children combined. IQR shifts in serum PFOS (15 to 28 ng/mL) and serum PFNA (1.2 to 2 ng/mL) were both associated with a 0.011 increase in TT4 in children 44578 years old (95% CIs: 0.6, 1.5 and 0.7, 1.5 respectively).CONCLUSIONS: This is the first large-scale report in children suggesting associations of serum PFOS and PFNA with thyroid hormone levels and of serum PFOA and hypothyroidism.	●	●	●	●	●	●			-	1	A	A

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献クラン①抽出	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
978	ヒト（内分泌系）	Melzer, D.; Rice, N.; Depledge, M. H.; Henley, W. E.; Galloway, T. S.	Association between serum perfluorooctanoic acid (PFOA) and thyroid disease in the U	2010	Environ Health Perspect. 2010 May;118(5):686-92. doi: 10.1289/ehp.0901584. Epub 2010 Jan 7.	Background: Perfluorooctanoic acid (PFOA, also known as C8) and perfluorooctane sulfonate (PFOS) are stable compounds with many industrial and consumer uses. Their persistence in the environment plus toxicity in animal models has raised concern over low-level chronic exposure effects on human health. Objectives: We estimated associations between serum PFOA and PFOS concentrations and thyroid disease prevalence in representative samples of the U.S. general population. Methods: Analyses of PFOA/PFOS versus disease status in the National Health and Nutrition Examination Survey (NHANES) for 1999-2000, 2003-2004, and 2005-2006 included 3,974 adults with measured concentrations for perfluorinated chemicals. Regression models were adjusted for age, sex, race/ethnicity, education, smoking status, body mass index, and alcohol intake. Results: The NHANES-weighted prevalence of reporting any thyroid disease was 16.18% (n = 292) in women and 3.06% (n = 69) in men; prevalence of current thyroid disease with related medication was 9.89% (n = 163) in women and 1.88% (n = 46) in men. In fully adjusted logistic models, women with PFOA >or= 5.7 ng/mL [fourth (highest) population quartile] were more likely to report current treated thyroid disease [odds ratio (OR) = 2.24; 95% confidence interval (CI), 1.38-3.65; p = 0.002] compared with PFOA <or= 4.0 ng/mL (quartiles 1 and 2); we found a near significant similar trend in men (OR = 2.12; 95% CI, 0.93-4.82; p = 0.073). For PFOS, in men we found a similar association for those with PFOS >or= 36.8 ng/mL (quartile 4) versus <or= 25.5 ng/mL (quartiles 1 and 2: OR for treated disease = 2.68; 95% CI, 1.03-6.98; p = 0.043); in women this association was not significant. Conclusions: Higher concentrations of serum PFOA and PFOS are associated with current thyroid disease in the U.S. general adult population. More work is needed to establish the mechanisms involved and to exclude confounding and pharmacokinetic explanations.	●	●		●	●	●				-		1	B	A
979	ヒト（内分泌系）	Preston, E. V.; Webster, T. F.; Oken, E.; Claus Henn, B.; Mcclean, M. D.; Rifas-Shiman, S. L.; Pearce, E. N.; Braverman, L. E.; Calafat, A. M.; Ye, X.; Sagiv, S. K.	Maternal plasma per- and polyfluoroalkyl substance concentrations in early pregnancy and maternal and neonatal thyroid function in a prospective birth cohort: Project Viva (USA)	2018	Environ Health Perspect. 2018 Feb 27;126(2):027013. doi: 10.1289/EHP2534.	BACKGROUND: Prenatal exposure to some per- and polyfluoroalkyl substances (PFASs) may disrupt maternal and neonatal thyroid function, which is critical for normal growth and neurodevelopment.OBJECTIVES: We examined associations of PFAS exposure during early pregnancy with maternal and neonatal thyroid hormone levels.METHODS: We studied 732 mothers and 480 neonates in Project Viva, a longitudinal prebirth cohort in Boston, Massachusetts. We quantified six PFASs, including perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), and maternal thyroid hormones [thyroxine (T4), Free T4Index (FT4I), thyroid stimulating hormone (TSH)] in plasma samples collected at a median 9.6 wk gestation and neonatal T4levels from postpartum heel sticks. We estimated associations of PFAS concentrations with thyroid hormone levels using covariate-adjusted linear regression models and explored effect measure modification by maternal thyroid peroxidase antibody (TPOAb) status and infant sex.RESULTS: PFAS concentrations were not associated with maternal T4, but PFOA, perfluorohexane sulfonate (PFHxS), and 2-(N-methyl-perfluorooctane sulfonamido) acetate (MeFOSAA) were inversely associated with maternal FT4I [e.g., -0.0187 (95% confidence interval (CI): -3.40, -0.31) per interquartile (IQR) increase in PFOA]. PFAS concentrations [PFOA, PFOS, and perfluorononanoate (PFNA)] were inversely associated with TSH levels in TPOAb-positive women only. Prenatal PFOS, PFOA, and PFHxS concentrations were inversely associated with T4levels in male [e.g., PFHxS, quartile 4 vs.1: -2.51μg/dL (95% CI: -3.99, -1.04)], but not female neonates [0.40μg/dL (95% CI: -0.98, 1.79)].CONCLUSIONS: In this study, prenatal exposure to some PFASs during early pregnancy was inversely associated with maternal FT4I and neonatal T4in male infants. These results support the hypothesis that prenatal exposure to PFASs influences thyroid function in both mothers and infants.	●	●		●						-			B	B
980	ヒト（内分泌系）	Reardon, A. J. F.; Khodayari Moez, E.; Dinu, I.; Goruk, S.; Field, C. J.; Kinniburgh, D. W.; Macdonald, A. M.; Martin, J. W.; APrON Study	Longitudinal analysis reveals early-pregnancy associations between perfluoroalkyl sulfonates and thyroid hormone status in a Canadian prospective birth cohort	2019	Environ Int. 2019 Aug;129:389-399. doi: 10.1016/j.envint.2019.04.023. Epub 2019 May 28.	Serum perfluoroalkyl acids (PFAAs) have been linked to disruption of maternal thyroid hormone homeostasis, but results have varied between studies which we hypothesized was due to timing of the thyroid hormone measurements, variability in PFAA isomer patterns, or presence of other stressors. In a longitudinal study design, we investigated the time-dependency of associations between PFAA isomers and thyroid hormones during pregnancy and post-partum while considering thyroid peroxidase antibody (TPOAb) status and mercury (Hg) co-exposure. In participants of a prospective Canadian birth cohort (n = 494), free thyroxine (FT4), free triiodothyronine (FT3), thyroid stimulating hormone (TSH) and TPOAb were quantified in maternal plasma collected in each trimester and 3-months postpartum, and 25 PFAAs (15 linear and 10 branched) and Hg were quantified in samples collected during the second trimester. Perfluorohexane sulfonate (PFHxS) and total branched isomers of perfluorooctane sulfonate (PFOS) were positively associated with TSH in mixed-effect models, with strongest associations early in gestation. Throughout pregnancy and post-partum, PFHxS was inversely associated with FT4, consistent with elevated TSH, while Hg was inversely associated with FT3. In TPOAb-positive women, negative associations were found between PFUnA and FT4, and 1m-PFOS and TSH, supporting previous studies that thyroid disorder could increase susceptibility to PFAA-mediated hormone dysregulation. Hg did not confound associations but was a significant interaction term, revealing further positive associations between PFOS isomers (∑3m+4m-PFOS) and TSH. Higher perfluoroalkyl sulfonate exposures were associated with higher TSH and/or lower FT4, strongly suggestive that PFHxS and branched PFOS isomers are risk factors for subclinical maternal hypothyroidism. Isomer-specific analysis is important in future studies, as crude measures of total-PFOS' masked the associations of branched isomers. A concerning result was for PFHxS which had consistent negative associations with FT4 at all time points and a positive association with TSH in early pregnancy when fetal development is most sensitive to disruption.	●	●								-			B	B
981	ヒト（内分泌系）	Shah-Kulkarni, S.; Kim, B. M.; Hong, Y. C.; Kim, H. S.; Kwon, E. J.; Park, H.; Kim, Y. J.; Ha, E. H.	Prenatal exposure to perfluorinated compounds affects thyroid hormone levels in newborn girls	2016	Environ Int. 2016 Sep;94:607-613. doi: 10.1016/j.envint.2016.06.024. Epub 2016 Jul 7.	Perfluorinated compounds (PFCs) are ubiquitous in the environment and have been detected in humans and wildlife. Exposure to PFCs has decreased in the United States recently, while exposure to PFCs continues in Asian countries, which represents a public health concern. Various mechanisms by which PFCs affect fetal growth have been proposed, such as activation of peroxisome proliferators, disruption of thyroid hormones and changes in lipid metabolism. However, the overall evidence for an association with thyroid hormones is not strong. Therefore, we examined the effect of various prenatal PFCs on cord blood thyroid hormones: triiodothyronine (T3), thyroxine (T4), thyroid stimulating hormone (TSH) levels, and explored the endocrine disrupting effect of these PFCs on thyroid hormone levels in children according to gender. Two hundred and seventy-nine study participants were selected from among the enrolled participants in the Ewha Birth & Growth Retrospective Cohort, a retrospective birth cohort study conducted at Ewha Womans University Hospital, Seoul, Korea between 2006 and 2010 A generalized linear model was constructed to explore the association of PFCs and thyroid hormones. Further, an analysis stratified by gender was conducted. Our study shows that cord blood perfluoro n-pentanoic acid (PFPeA) was positively associated with cord blood T4 (p=0.01) level. Gender-specific analysis showed that prenatal PFCs: PFPeA and Perfluorohexane sulfonic acid (PFHxS) exposure significantly increased T4 (p<0.01) and T3 (p=0.03), respectively, while perfluorononanoic acid (PFNA) decreased TSH (p=0.04) concentration in newborn girls. Thus, prenatal PFC exposure may disrupt thyroid hormone homeostasis. Thyroid hormones play a crucial role in fetal development and may have gender specific action. Hence, these results are of utmost importance in high-risk groups, such as pregnant women and children.	●	●	●	●						-			B	B
982	ヒト（内分泌系）	Shrestha, Srishti; Bloom, Michael S; Yucel, Recai; Seegal, Richard F; Wu, Qian; Kannan, Kurunthachalam; Rej, Robert; Fitzgerald, Edward F	Perfluoroalkyl substances and thyroid function in older adults	2015	Environ Int. 2015 Feb;75:206-14. doi: 10.1016/j.envint.2014.11.018. Epub 2014 Dec 5.	Current understanding of the thyroid disruptive properties of perfluoroalkyl substances (PFASs), particularly in aging populations, is limited. The objectives of this study were to (i) assess associations between thyroid function, as measured by serum thyrotropin (thyroid stimulating hormone, TSH), free thyroxine (fT4), total thyroxine (T4), and total triiodothyronine (T3), and serum perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) in an aging population and (ii) determine if other persistent organic pollutants with thyroid disruptive properties including polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) modify such associations. We conducted a cross-sectional study of 87 men and women 55 to 74years of age, without clinically-diagnosed thyroid disease, who resided in upper Hudson River communities in New York. Geometric means (standard deviations) of serum PFOS and PFOA were 31.6 (1.7) ng/mL and 9.17 (1.72) ng/mL, respectively. Multivariable linear regression analyses indicated that one interquartile range difference in PFOS corresponded to 4% and 9% increases in fT4 and T4 respectively. We detected statistical interactions between PFOA and age for effects on fT4 and T4; joint increases in PFOA and age were associated with increases in fT4 and T4, of 3% and 7%, respectively. We also detected statistical interactions between PFOS and total PCBs for the effect on T3 and between PFOA and total PBDEs for the effect on TSH. Our results suggest that PFASs are associated with subtle alterations in thyroid hormone levels in this population, and that these associations are likely to vary by age, and levels of PCBs and PBDEs.	●	●		●						-			B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報抽出対象	文献ランク①	文献ランク②
983	ヒト（内分泌系）	Singer, A. B.; Whitworth, K. W.; Haug, L. S.; Sabaredzovic, A.; Impinen, A.; Papadopoulou, E.; Longnecker, M. P.	Menstrual cycle characteristics as determinants of plasma concentrations of perfluoroalkyl substances (PFASs) in the Norwegian Mother and Child Cohort (MoBa study)	2018	Environ Res. 2018 Oct;166:78-85. doi: 10.1016/j.envres.2018.05.019. Epub 2018 Jun 4.	INTRODUCTION: Perfluoroalkyl substances (PFASs) are fluorinated organic compounds that have been used in a variety of industrial and consumer applications. Menstruation is implicated as a possible route of elimination for PFASs in women. The overall purpose of this study was to examine menstrual cycle characteristics as determinants of plasma PFAS concentrations in women.METHODS: Our study sample consisted of 1977 pregnant women from the Norwegian Mother and Child Cohort (MoBa) study. The women were asked about menstrual cycle regularity in the year before the pregnancy and typical menstrual cycle length as well as other demographic and reproductive characteristics in a questionnaire completed during the pregnancy. Blood samples were collected around 17-18 weeks gestation and PFAS concentrations were measured in plasma. We examined the association between menstrual cycle characteristics and seven PFASs (perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), perfluorohexane sulfonate (PFHxS), perfluoroheptane sulfonate (PFHpS), and perfluorooctane sulfonate (PFOS)) using multiple linear regression, adjusted for age, pre-pregnancy body mass index, smoking, education, income, parity, oral contraceptive use, inter-pregnancy interval, and breastfeeding duration.RESULTS: Irregular cycles were not associated with PFAS concentrations. Overall, we found no evidence of associations between menstrual cycle length and PFAS concentrations. In subgroup analyses we found some evidence, among parous women, of decreased PFHpS and PFOS with short menstrual cycles; we also found, among recent OC users (in the 12 months before the questionnaire) increased PFNA and PFUnDA with long cycle length. Limitations of our study include misclassification of menstrual cycle characteristics, small sample sizes in the sub-group analyses, and a lack of information on duration and volume of menses.CONCLUSIONS: In the entire study sample, we found little evidence of menstrual cycle characteristics as determinants of PFAS concentrations. However, we observed some associations between cycle length and PFAS concentrations with some select PFAS compounds in subgroup analyses.	●	●	●							-		B	B
984	ヒト（内分泌系）	Song, X.; Tang, S.; Zhu, H.; Chen, Z.; Zang, Z.; Zhang, Y.; Niu, X.; Wang, X.; Yin, H.; Zeng, F.; He, C.	Biomonitoring PFAAs in blood and semen samples: Investigation of a potential link between PFAAs exposure and semen mobility in China	2018	Environ Int. 2018 Apr;113:50-54. doi: 10.1016/j.envint.2018.01.010. Epub 2018 Feb 6.	Perfluoroalkyl acids (PFAAs) have been suspected to act as endocrine disruptors and adversely affect human reproductive health. We aimed to investigate the association between PFAAs in blood and semen, explore a potential link between PFAAs exposure and semen quality in the population of the Pearl River Delta (PRD) region in China, one of the "world factories". The monitoring results demonstrated that the population (103 male participants) from the PRD region in this study had higher PFAAs levels in blood and semen than some other areas in China. PFOS was found at the highest mean concentrations of 118.16 ng/mL in blood and 5.31 ng/mL in semen among the nine PFAAs. Significant associations were found between concentrations of several analytes in blood and semen, including Σ9 PFAAs ($r = 0.475$, $P < .01$), PFOA ($r = 0.215$, $P = .029$), PFHS ($r = 0.458$, $P < .01$) and PFOS ($r = 0.981$, $P < .01$). BMI was the most important factor to PFAAs, but there was no significant difference in PFAAs concentrations in blood and semen collected from participants with different smoking and drinking habits, education background and occupations. Negative correlations were significantly observed between sperm motility and PFBA, PFPeA, PFHxA, PFBS, PFOA, PFHS, PFOS and Σ9PFAAs in semen. Therefore, exposure to PFAAs may result in a decline in semen mobility in participants from the PRD region.	●	●	●							-		B	B
985	ヒト（内分泌系）	Taylor, K. W.; Hoffman, K.; Thayer, K. A.; Daniels, J. L.	Polyfluoroalkyl chemicals and menopause among women 20-65 years of age (NHANES)	2014	Environ Health Perspect. 2014 Feb;122(2):145-50. doi: 10.1289/ehp.1306707. Epub 2013 Nov 26.	background: Polyfluoroalkyl chemicals (PFCs) such as perfluorooctane sulfonate (PFOS) and perfluoro-octanoate (PFOA) have been associated with early menopause. However, previous crosssectional studies have lacked adequate data to investigate possible reverse causality (i. e., higher serum concentrations due to decreased excretion after menopause).	●	●	●	●						-		D	B
986	ヒト（内分泌系）	Timmermann, C. A.; Budtz-Jørgensen, E.; Petersen, M. S.; Weihe, P.; Steuerwald, U.; Nielsen, F.; Jensen, T. K.; Grandjean, P.	Shorter duration of breastfeeding at elevated exposures to perfluoroalkyl substances	2017	Reprod Toxicol. 2017 Mar;68:164-170. doi: 10.1016/j.reprotox.2016.07.010. Epub 2016 Jul 12.	The aim of this study was to determine whether maternal exposure to persistent perfluoroalkyl substances (PFASs) affect the capability to breastfeed. In two Faroese birth cohorts (N=1130), concentrations of five PFASs were measured in maternal serum during pregnancy or two weeks after term. Duration of breastfeeding was assessed by questionnaire and clinical interview. In adjusted linear regression models, a doubling of maternal serum PFASs was associated with a reduction in duration of both total and exclusive breastfeeding, most pronounced for perfluorooctane sulfonic acid (PFOS) where a doubling was associated with a reduction in total breastfeeding of 1.4 (95% CI: 0.6; 2.1) months and perfluorooctanoic acid (PFOA) where a doubling was associated with a reduction in exclusive breastfeeding of 0.5 (0.3; 0.7) months. The associations were evident among both primiparous and multiparous women, and thus cannot be explained by confounding from previous breastfeeding.	●	●	●	●		●				-		D	B
987	ヒト（内分泌系）	Toft, G; Jönsson, BAG; Lindh, CH; Giwercman, A; Spano, M; Heederik, D; Lenters, V; Vermeulen, R; Rylander, L; Pedersen, HS; Ludwicki, JK; Zviezdai, V; Bonde, JP.	Exposure to perfluorinated compounds and human semen quality in arctic and European populations	2012	Hum Reprod. 2012 Aug;27(8):2532-40. doi: 10.1093/humrep/des185. Epub 2012 May 30.	BACKGROUND: Perfluorinated compounds (PFCs) have been suspected to adversely affect human reproductive health. The aim of this study was to investigate the associations between PFC exposure and male semen quality. METHODS: PFCs were measured in serum from 588 partners of pregnant women from Greenland, Poland and Ukraine who provided a semen sample, using liquid chromatography tandem mass spectrometry. Perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), perfluorohexane sulfonic acid (PFHxS) and perfluorononanoic acid (PFNA) could be detected in >97% of the samples. The associations between levels of these compounds and semen volume, sperm concentration, total sperm count, motility and morphology were assessed. RESULTS: Across countries, sperm concentration, total sperm count and semen volume were not consistently associated with PFOS, PFOA, PFHxS or PFNA levels. The proportion of morphologically normal cells was 35% lower [95% confidence interval (CI): 4-66%) for the third tertile of PFOS exposure as compared with the first. A similar reduction was found in relation to increasing PFHxS levels. At the third PFOA exposure tertile, the percentage of motile spermatozoa was 19% (95% CI: 1 to 39%) higher than in the first. CONCLUSIONS: The most robust finding in the present study was the negative associations between PFOS exposure and sperm morphology suggesting adverse effects of PFOS on semen quality, possibly due to interference with the endocrine activity or sperm membrane function. It cannot be excluded that this association and the positive association between PFOA and semen motility, which was not consistent across countries, might represent a chance finding due to the multiple statistical tests being performed.	●	●	●	●	●	●			●	-	1	A	B
988	ヒト（内分泌系）	Tsai, M. S.; Lin, C. C.; Chen, M. H.; Hsieh, W. S.; Chen, P. C.	Perfluoroalkyl substances and thyroid hormones in cord blood	2017	Environ Pollut 222: 543-548. doi: 10.1016/j.envpol.2016.11.027. Epub 2016 Dec 23.	BACKGROUND: Perfluoroalkyl substances (PFASs) are pollutants that tend to accumulate in the environment and organisms. The animal and human studies to date have focused on thyroid function, but the results are inconsistent.METHODS: A sample of 118 mother-infant pairs was obtained from the Taiwan Birth Panel Study (TBPS). Cord blood PFASs levels were evaluated using the Waters ACQUITY UPLC system coupled with a Waters Quattro Premier XE triple quadrupole mass spectrometer, and cord blood thyroid hormones were assessed using a Roche Analytics E170 modular analyser (Roche Diagnostics, Mannheim, Germany). PFASs concentrations were analysed in the final models to examine the associations between cord blood PFASs levels and thyroid hormone concentrations.RESULTS: The cord blood perfluorooctane sulfonate (PFOS) concentration was negatively associated with the cord blood thyroxine (T4) concentration [per ln unit: adjusted β (95% confidence interval, CI) = -0.458(-0.916, -0.001)]. Moreover, the level of cord blood thyroid stimulating hormone (TSH) was positively associated with the cord blood PFOS concentration [per ln unit: adjusted β (95% confidence interval, CI) = 0.346(0.101, 0.592)]. The sex stratified effects of PFOS on T4 were suggestive of differential effects in high-exposure groups compared with low-exposure group in boys.CONCLUSIONS: We found that cord blood thyroid hormone levels are affected by PFASs, with a negative association between T4 and PFOS and a positive association between TSH and PFOS. The causal associations of thyroid hormones and PFASs require further exploration.	●	●		●						-		B	B
989	ヒト（内分泌系）	Wang, Wei; Zhou, Wei; Wu, Shaowei; Liang, Fan; Li, Yan; Zhang, Jun; Cui, Linlin; Feng, Yan; Wang, Yan	Perfluoroalkyl substances exposure and risk of polycystic ovarian syndrome related infertility in Chinese women	2019	Environ Pollut. 2019 Apr;247:824-831. doi: 10.1016/j.envpol.2019.01.039. Epub 2019 Jan 11.	Perfluoroalkyl substances (PFASs) are a family of synthetic, fluorinated organic compounds. They have been widely used in industrial applications and consumer products and widespread in the environment, wildlife and human. Experimental and epidemiologic evidence suggested that PFASs are capable of interfering with endocrine processes and have potential reproductive and developmental toxicities. Polycystic ovarian syndrome (PCOS), one of the main reasons of female infertility, is a common endocrine disorder in reproductive age women. We performed a case-control study to evaluate associations between PCOS-related infertility and PFASs concentrations in plasma. A total of 180 infertile PCOS-cases and 187 healthy controls were recruited from the Center for Reproductive Medicine of Shandong University. Blood specimens were collected at enrollment and analyzed for ten PFASs using liquid chromatography-tandem mass spectrometry. Multivariable logistic regression procedure was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for each PFAS. Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) were the dominant PFASs in the plasma of participants, with the median concentration of 5.07 ng/mL and 4.05 ng/mL, respectively. The median levels of individual PFAS were not significantly different between PCOS-cases and controls. While adjusted for the potential confounders (age, BMI, household income, education level, employment status, age at menarche, menstrual volume), the plasma concentration of perfluorododecanoic acid (PFDoA), a 12 carbons lengths of perfluorocarboxylic acids, was associated with a significantly increased risk of PCOS-related infertility (medium vs low tertile: $OR = 2.36$, 95% CI: 1.12, 4.99, $P = 0.02$; high vs low tertile: $OR = 3.04$, 95% CI: 1.19, 7.67, $P = 0.02$), with the P trend 0.01. No significant relationship was observed between PCOS-related infertility and other PFAS analytes in the adjusted model, despite perfluoroundecanoic acid showed a negative association (P trend 0.03). The potential reproductive health effects of PFASs and the underlying mechanisms merit further investigation in the future.	●	●	●							-		B	B
990	ヒト（内分泌系）	Wang, Y.; Rogan, W. J.; Chen, P. C.; Lien, G. W.; Chen, H. Y.; Tseng, Y. C.; Longnecker, M. P.; Wang, S. L.	Association between maternal serum perfluoroalkyl substances during pregnancy and maternal and cord thyroid hormones: Taiwan maternal and infant cohort study	2008	Environ Health Perspect. 2014 May;122(5):529-34. doi: 10.1289/ehp.1306925. Epub 2014 Feb 21.	BACKGROUND: Perfluoroalkyl substances (PFASs) are synthetic compounds that are widely used in industry and are often detectable in humans. In pregnant rats and their pups, PFASs can interfere with thyroid hormone homeostasis. In humans, maternal thyroid hormones supply the fetus throughout pregnancy, and thyroid hormones play a critical role in fetal growth and neurodevelopment.	●	●	●	●						-		D	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
991	ヒト（内分泌系）	Wang, Y.; Starling, A. P.; Haug, L. S.; Eggesbo, M.; Becher, G.; Thomsen, C.; Travlos, G.; King, D.; Hoppin, J. A.; Rogan, W. J.; Longnecker, M. P.	Association between perfluoroalkyl substances and thyroid stimulating hormone among pregnant women: a cross-sectional study	2013	Environ Health. 2013 Sep 8;12(1):76. doi: 10.1186/1476-069X-12-76.	BACKGROUND: Perfluoroalkyl substances (PFASs) are a group of highly persistent chemicals that are widespread contaminants in wildlife and humans. Exposure to PFAS affects thyroid homeostasis in experimental animals and possibly in humans. The objective of this study was to examine the association between plasma concentrations of PFASs and thyroid stimulating hormone (TSH) among pregnant women. METHODS: A total of 903 pregnant women who enrolled in the Norwegian Mother and Child Cohort Study from 2003 to 2004 were studied. Concentrations of thirteen PFASs and TSH were measured in plasma samples collected around the 18th week of gestation. Linear regression models were used to evaluate associations between PFASs and TSH. RESULTS: Among the thirteen PFASs, seven were detected in more than 60% of samples and perfluorooctane sulfonate (PFOS) had the highest concentrations (median, 12.8 ng/mL; inter-quartile range [IQR], 10.1 -16.5 ng/mL). The median TSH concentration was 3.5 (IQR, 2.4 - 4.8) μIU/mL. Pregnant women with higher PFOS had higher TSH levels. After adjustment, with each 1 ng/mL increase in PFOS concentration, there was a 0.8% (95% confidence interval: 0.1%, 1.6%) rise in TSH. The odds ratio of having an abnormally high TSH, however, was not increased, and other PFASs were unrelated to TSH. CONCLUSIONS: Our results suggest an association between PFOS and TSH in pregnant women that is small and may be of no clinical significance.	●	●	●							-		B	B
992	ヒト（内分泌系）	Webster, G. M.; Venners, S. A.; Mattman, A.; Martin, J. W.	Associations between perfluoroalkyl acids (PFASs) and maternal thyroid hormones in early pregnancy: a population-based cohort study	2014	Environ Res. 2014 Aug;133:338-47. doi: 10.1016/j.envres.2014.06.012. Epub 2014 Jul 12.	BACKGROUND: Associations between perfluoroalkyl acids (PFASs) and human thyroid hormone levels remain unclear, especially during early pregnancy when small changes in maternal thyroid hormones can affect fetal brain development.OBJECTIVES: To examine associations between maternal serum PFAS levels and maternal thyroid hormone levels in the early 2nd trimester of pregnancy.METHODS: Participants were euthyroid pregnant women (n=152) enrolled in the Chemicals, Health and Pregnancy (CHirP) study based in Vancouver, Canada. Associations between maternal serum PFASs, including perfluorohexanesulfonate (PFHxS), perfluorononanoate (PFNA), perfluorooctanoate (PFOA) and perfluorooctanesulfonate (PFOS) and repeated measures of maternal thyroid hormones, including free thyroxine (fT4), total thyroxine (TT4) and thyroid stimulating home (TSH) were examined using mixed effects linear models. Associations were considered in all women, then separately in women with high (≥ 9 IU/mL) vs normal (<9 IU/mL) levels of thyroid peroxidase antibody (TPOAb), a marker of autoimmune hypothyroidism (Hashimoto's disease).RESULTS: Median PFAS concentrations (ng/mL) in maternal sera were 1 (PFHxS), 0.6 (PFNA), 1.7 (PFOA) and 4.8 (PFOS). PFASs were not associated with fT4, TT4 or TSH among women with normal TPOAb. However, among the 0.09 of women with high TPOAb (n=14), interquartile range (IQR) increases of PFASs were associated with a 46-69% increase in maternal TSH (95% CIs ranging from 0.08 to 123%) (PFNA, PFOA and PFOS only), and with a 0.03 to 0.07 decrease in maternal fT4 (95% CIs ranging from -0.18 to 5%) (all 4 PFASs). PFNA was also associated with higher maternal TSH in the whole sample.CONCLUSIONS: PFASs were positively associated with TSH, and weakly negatively associated with fT4 in the subset of pregnant women with high TPOAb, which occurs in 6-10% of pregnancies. PFASs may exacerbate the already high TSH and low fT4 levels in these women during early pregnancy, which is a critical time of thyroid hormone-mediated fetal brain development. The clinical significance of these findings is not clear. We propose a "multiple hit hypothesis" to explain these findings; this hypothesis deserves evaluation in larger, more representative study samples.	●	●	●							-		B	B
993	ヒト（内分泌系）	Wen, L. L.; Lin, L. Y.; Su, T. C.; Chen, P. C.; Lin, C. Y.	Association between serum perfluorinated chemicals and thyroid function in U	2013	J Clin Endocrinol Metab. 2013 Sep;98(9):E1456-64. doi: 10.1210/jc.2013-1282. Epub 2013 Jul 17.	CONTEXT: Perfluorinated chemicals (PFCs) have been widely used in a variety of products worldwide for years. The relationship between serum PFCs and thyroid function has never been addressed in a nationally representative survey.OBJECTIVES: The study examined the association between serum PFCs and thyroid function in the general U.S. population.DESIGN AND PARTICIPANTS: We selected 1181 subjects (aged >20 years) from a National Health and Nutrition Examination Survey (NHANES) in 2007 through 2008 and 2009 through 2010 to determine the relationship between serum PFCs and thyroid function. Data were adjusted for confounding variables.RESULTS: The geometric means and 0.95 confidence interval (CI) concentrations of perfluorooctanoate (PFOA), perfluorooctane sulfonate, perfluorononanoic acid, and perfluorohexane sulfonate (PFHxS) were 4.15 (4.02-4.29), 14.2 (13.59-14.86), 1.54 (1.48-1.59), and 2 (1.89-2.11) ng/mL, respectively. After weighting for sampling strategy, we determined a 1-U increase in natural log-serum PFOA increased serum total T3 concentration by 6.628 ng/dL (95% CI = 0.545-12.712, P = .035) in women. A 1-U increase in natural log-PFHxS was associated with an increase of total T4 by 0.26 μg/mL (95% CI = 0.108-0.413, P = .002) and total T3 by 4.074 ng/dL (95% CI = 2.232-5.916, P < .001) in women and a decrease of natural log-free T4 by 0.016 (ng/dL) (95% CI = -0.029 to 0.003, P = .019) in men.CONCLUSION: Higher serum concentrations of PFOA and PFHxS are associated with total T3, total T4, and free T4 in the U.S. general population. More studies are warranted to clarify the causal relationship between PFCs and thyroid function.	●	●	●	●					●	-		B	B
994	ヒト（内分泌系）	Winquist, A; Steenland, K.	Perfluorooctanoic acid exposure and thyroid disease in community and worker cohorts	2014	Epidemiology 25: 255-264. doi: 10.1097/EDE.0000000000000040.	BACKGROUND: Perfluorooctanoic acid (PFOA) was released from a mid-Ohio River Valley chemical plant, exposing the surrounding community to PFOA for >50 years, primarily through drinking water. Toxicological studies and some previous human studies have suggested that PFOA can disrupt thyroid homeostasis. We examined the association between PFOA and thyroid disease among community members and plant workers. METHODS: Participants completed health surveys during 2008-2011. Yearly serum PFOA concentrations were estimated for each participant starting at birth or in 1952, whichever came later. We used Cox proportional hazard models, stratified by birth year, to assess adult thyroid disease hazard in relation to time-varying yearly or cumulative (sum of yearly estimates) estimated PFOA serum concentration, controlling for sex, race, education, smoking, and alcohol use. RESULTS: Of 32,254 participants, 3,633 reported functional thyroid disease (excluding neoplasms, congenital disease, nodules without functional changes, cysts, and unspecified type). Analyses were restricted to 2109 cases of functional thyroid disease with thyroid prescription medication use and validation through medical record review. In analyses starting at age 20 years or in 1952, thyroid disease hazard ratios across cumulative exposure quintiles were 1.00, 1.24, 1.27, 1.36, and 1.37 among women and 1.00, 1.12, 0.83, 1.01, and 1.05 among men (log-linear trend tests: P = 0.03 and P = 0.85, respectively); similar results were observed for yearly exposure. Associations were observed for hyperthyroidism and hypothyroidism among women. Some subanalyses also suggested an increased hazard of hypothyroidism among men.	●	●		●						-		B	B
995	ヒト（内分泌系）	Yang, L.; Li, J.; Lai, J.; Luan, H.; Cai, Z.; Wang, Y.; Zhao, Y.; Wu, Y.	Placental transfer of perfluoroalkyl substances and associations with thyroid hormones: Beijing prenatal exposure study	2016	Sci Rep. 2016 Feb 22;6:21699. doi: 10.1038/srep21699.	Perfluoroalkyl substances (PFASs) have been detected in wildlife and human samples worldwide. Toxicology research showed that PFASs could interfere with thyroid hormone homeostasis. In this study, eight PFASs, fifteen PFAS precursors and five thyroid hormones were analyzed in 157 paired maternal and cord serum samples collected in Beijing around delivery. Seven PFASs and two precursors were detected in both maternal and cord sera with significant maternal-fetal correlations ($r = 0.336$ to 0.806, all $P < 0.001$). The median ratios of major PFASs concentrations in fetal versus maternal serum were from 0.25:1 (perfluorodecanoic acid, PFDA) to 0.65:1 (perfluorooctanoic acid, PFOA). Spearman partial correlation test showed that maternal thyroid stimulating hormone (TSH) was negatively correlated with most maternal PFASs ($r = -0.261$ to -0.170, all $P < 0.05$). Maternal triiodothyronin (T3) and free T3 (FT3) showed negative correlations with most fetal PFASs ($r = -0.229$ to -0.165 for T3; $r = -0.293$ to -0.169 for FT3, all $P < 0.05$). Our results suggest prenatal exposure of fetus to PFASs and potential associations between PFASs and thyroid hormone homeostasis in humans.	●	●	●	●						-		B	B
996	ヒト（内分泌系）	Yao, Q.; Shi, R.; Wang, C.; Han, W.; Gao, Y.; Zhang, Y.; Zhou, Y.; Ding, G.; Tian, Y.	Cord blood per- and polyfluoroalkyl substances, placental steroidogenic enzyme, and cord blood reproductive hormone	2019	Environ Int. 2019 Aug;129:573-582. doi: 10.1016/j.envint.2019.03.047. Epub 2019 Jun 4.	Background: Per- and polyfluoroalkyl substances (PFASs) are widely used in China, but little is known about the association between prenatal PFASs exposure and fetal reproductive development as well as its potential mechanism. Objective: We investigated the effects of cord blood PFASs on fetal reproductive hormones and its potential mechanism in relation to steroidogenic enzymes. Methods: Ten selected PFASs (n = 351) including PFOS, PFOA, PFBS, PFDA, PFDoA, PFHpA, PFHxS, PFNA, PFOSA, and PFUA, and two reproductive hormones estradiol (E2) (n = 351) and testosterone (T) (n = 349) were measured in 351 cord blood serum samples from a Chinese birth cohort between 2010 and 2013. Three steroidogenic enzymes including P450arom (n = 125), 3β-HSD1 (n = 123), and 17β-HSD1 (n = 116) were measured in 125 placental tissue samples. Linear regression tested the associations between cord blood PFASs and reproductive hormones in cord blood. Mediation analysis assessed the role of placental steroidogenic enzymes between cord blood PFASs and reproductive hormones. Results: The positive associations between PFOA, PFHxS and E2 levels, PFOS, PFUA, PFNA and T levels, and PFOS, PFUA and T/E2 ratio were significant. PFUA, PFNA, PFDA, PFHxS, and ΣPFASs were associated with higher P450arom levels. PFHxS was also associated with increased 3β-HSD1 and 17β-HSD1 levels. These associations were more pronounced in females than males when stratified by gender. Furthermore, 17β-HSD1 demonstrated mediating effects in the positive association between cord blood PFHxS and E2 levels in females. Conclusion: Our findings suggested the potential impacts of cord blood PFASs on fetal reproductive hormones, in which steroidogenic enzymes may play important roles. These associations were more pronounced in females than males.	●	●	●							アブスト入力もれ、要確認	1	D	D

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
997	ヒト（内分泌系）	Zhang, S.; Tan, R.; Pan, R.; Xiong, J.; Tian, Y.; Wu, J.; Chen, L.	Association of perfluoroalkyl and polyfluoroalkyl substances with premature ovarian insufficiency in Chinese women	2018	J Clin Endocrinol Metab. 2018 Jul 1;103(7):2543-2551. doi: 10.1210/jc.2017-02783.	Context: Perfluoroalkyl and polyfluoroalkyl substances (PFASs), a group of ubiquitous environmental chemicals with properties of endocrine disruption, are often detectable in humans.Objective: The current study investigated the association between exposure to PFAS and primary ovarian insufficiency (POI).Design, Patients, Interventions, and Main Outcome Measures: Levels of plasma PFAS were measured in 120 Chinese women with overt POI and 120 healthy control subjects from 2013 to 2016 Associations between PFAS levels and odds of POI, as well as hormonal profiles, were evaluated using multiple logistic regression and multiple linear regression models.Results: Levels of perfluorooctanate (PFOA), perfluorooctane sulfonate (PFOS), and perfluorohexanesulfonate (PFHxS) were positively associated with the risks of POI (highest vs. lowest tertile, PFOA: OR, 3.80; 0.95 CI, 1.92-7.49; PFOS: OR, 2.81; 0.95 CI, 1.46-5.41; PFHxS: OR, 6.63; 0.95 CI, 3.22-13.65). In patients with POI, levels of PFOS and PFHxS exposure were positively associated with FSH (PFOS: adjusted β, 0.26; 0.95 CI, 0.15 to 0.38; PFHxS: adjusted β, 0.16; 0.95 CI, 0.04 to 0.28) and negatively associated with estradiol (PFOS: adjusted β, -0.30; 0.95 CI, -0.47 to -0.12; PFHxS: adjusted β, -0.19; 0.95 CI, -0.37 to -0.02). Exposure to PFOS and PFOA was associated with elevation of prolactin (PFOS: adjusted β, 0.17; 0.95 CI, 0.06 to 0.29; PFOA: adjusted β, 0.16; 0.95 CI, 0.01 to 0.30) or with a decrease of free triiodothyronine (PFOS: adjusted β, -0.88; 0.95 CI, -1.64 to -0.09; PFOA: adjusted β, -0.90; 0.95 CI, -1.88 to 0.09) and thyroxine (PFOS: adjusted β, -2.99; 0.95 CI, -4.52 to -1.46; PFOA: adjusted β, -3.42; 0.95 CI, -5.39 to -1.46).Conclusion: High exposure to PFOA, PFOS, and PFHxS is associated with increased risk of POI in humans.	●	●	●							-	1	A	B
998	ヒト（内分泌系）	Zhou, Y.; Hu, L. W.; Qian, Z. M.; Geiger, S. D.; Parrish, K. L.; Dharmage, S. C.; Campbell, B.; Roponen, M.; Jalava, P.; Hirvonen, M. R.; Heinrich, J.; Zeng, X. W.; Yang, B. Y.; Qin, X. D.; Lee, Y. L.; Dong, G. H.	Interaction effects of polyfluoroalkyl substances and sex steroid hormones on asthma among children	2017	Sci Rep. 2017 Apr 18;7(1):899. doi: 10.1038/s41598-017-01140-5.	To evaluate the interactions between polyfluoroalkyl substances (PFASs) and reproductive hormones and associated asthma, a total of 231 asthmatic and 225 non-asthmatic adolescents were selected from northern Taiwan in the Genetic and Biomarkers study for Childhood Asthma from 2009-2010. The interaction between PFASs and reproductive hormones on asthma was analyzed with a two-level binary logistic regression model. The results showed that, among asthmatics, PFASs were positively associated with estradiol levels and negatively associated with testosterone levels. However, only significant association was identified for PFNA and estradiol in control group. After controlling for hormone levels, associations between PFAS exposure and asthma were consistently stronger among children with higher than lower estradiol, with odds ratios (OR) for asthma ranging from 1.25 for PFOS (95% Confidence Interval [CI]: 0.90, 1.72) to 4.01 for PFDA (95% CI: 1.46, 11.06) among boys and 1.25 for PFOS (95% CI: 0.84, 1.86) to 4.16 for PFNA (95% CI: 1.36, 12.73) among girls. Notably, the interactions between estradiol and PFASs were significant for PFOS (p = 0.026) and PFNA (p = 0.043) among girls. However, testosterone significantly attenuated the association between PFOS and asthma across sex. In conclusions, our findings suggested that reproductive hormones amplify the association between PFASs and asthma among adolescents.	●	●		●						-		B	B
999	ヒト（内分泌系）	Fei, Chunyuan; McLaughlin, Joseph K; Lipworth, Loren; Olsen, Jørn	Maternal concentrations of perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) and duration of breastfeeding	2010	Scand J Work Environ Health. 2010 Sep;36(5):413-21. doi: 10.5271/sjweh.2908. Epub 2010 Mar 3.	OBJECTIVE: Perfluorooctanoate (PFOA) has been associated with impaired lactation in mice. We examined whether maternal perfluorooctanesulfonate (PFOS) and PFOA concentrations correlated with duration of breastfeeding among women. METHODS: We randomly selected 1400 pregnant women from the Danish national birth cohort (1996-2002) and measured PFOS and PFOA concentrations in early pregnancy by using high performance liquid chromatography/tandem mass spectrometry. Self-reported data on the duration of any and exclusive breastfeeding were collected twice during telephone interviews around 6 and 18 months after the birth of the child. RESULTS: The duration of breastfeeding decreased with increasing concentrations of pregnancy PFOS and PFOA among multiparous women, for whom the adjusted odds ratios (OR) for weaning before 6 months of age were 1.20 (95% CI 1.06-1.37) per 10 ng/ml increase in PFOS concentrations and 1.23 (95% CI 1.13-1.33) per 1 ng/ml increase in PFOA concentrations. No consistent association was found for primiparous women. CONCLUSIONS: These findings suggest that PFOA and PFOS may reduce the ability to lactate, but could equally reflect reverse causation since no association was seen in primiparous women.			●		●	●				-		C	C
1000	ヒト（内分泌系）	Ji, Kyunghee; Kim, Sunmi; Kho, Younglim; Paek, Domyung; Sakong, Joon; Ha, Jongsik; Kim, Sungkyoon; Choi, Kyungho	Serum concentrations of major perfluorinated compounds among the general population in Korea: dietary sources and potential impact on thyroid hormones	2012	Environ Int. 2012 Sep 15;45:78-85. doi: 10.1016/j.envint.2012.03.007. Epub 2012 May 9.	Perfluorinated compounds (PFCs) have been frequently detected in both the environment and biota, and have become a growing concern. However, information is limited on the potential sources and human health implications of such exposure. We evaluated the exposure levels of 13 major PFCs among a population (n=633, >12 years of age) in a mid-sized city of Korea, and investigated for their potential dietary sources and the impact on thyroid hormone concentrations. For this purpose, we collected blood samples from a general population in Siheung, Korea and measured for 13 PFCs, total thyroxine (T4), and thyroid stimulating hormone (TSH). In addition, a questionnaire survey on diet was conducted. Perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorohexane sulfonic acid (PFHxS), and perfluorononanoic acid (PFNA) were detected in relatively greater concentrations than the other 9 PFCs in the blood serum. Males tend to have greater concentrations than females for most PFCs, and the concentrations were elevated as age increased up to 50s. Body mass index (BMI) was also shown to influence the serum concentrations of several PFCs. After adjustment for age, sex, and BMI, the consumption of vegetable, potato, fish/shellfish, and popcorn was identified to be significantly related with concentrations of major PFCs in blood. Among the studied PFCs, the concentrations of perfluorotridecanoic acid (PFTrDA) were negatively correlated with total T4, and positively with TSH levels, especially among females. The result of this study will provide information useful for developing public health and safety management measures for PFCs.			●	●						-		C	C
1001	ヒト（内分泌系）	Shelly, Colleen; Grandjean, Philippe; Oulhote, Youssef; Plomgaard, Peter; Frikke-Schmidt, Ruth; Nielsen, Flemming; Zmirou-Navier, Denis; Weihe, Pal; Valvi, Damaskini	Early life exposures to perfluoroalkyl substances in relation to adipokine hormone levels at birth and during childhood	2019	J Clin Endocrinol Metab. 2019 Nov 1;104(11):5338-5348. doi: 10.1210/jc.2019-00385.	BACKGROUND: Birth cohort studies have linked exposure to perfluoroalkyl substances (PFASs) with child anthropometry. Metabolic hormone dysregulation needs to be considered as a potential adverse outcome pathway. We examined the associations between PFAS exposures and concentrations of adipokine hormones from birth to adolescence. METHODS: We studied 80 mother-child pairs from a Faroese cohort born in 1997 to 2000. Five PFASs were measured in maternal pregnancy serum and in child serum at ages 5, 7, and 13 years. Leptin, adiponectin, and resistin were analyzed in cord serum and child serum at the same ages. We fitted multivariable-adjusted generalized estimating equations to assess the associations of PFASs at each age with repeated adipokine concentrations at concurrent and subsequent ages. RESULTS: We observed tendencies of inverse associations between PFASs and adipokine hormones specific to particular ages and sex. Significant associations with all adipokines were observed for maternal and child 5-year serum PFAS concentrations, whereas associations for PFASs measured at ages 7 to 13 years were mostly null. The inverse associations with leptin and adiponectin were seen mainly in females, whereas the inverse PFAS associations with resistin levels were seen mainly in males. Estimates for significant associations (P value <0.05) suggested mean decreases in hormone levels (range) by 38% to 89% for leptin, 16% to 70% for adiponectin, and 33% to 62% for resistin for each twofold increase in serum PFAS concentration. CONCLUSIONS: These findings suggest adipokine hormone dysregulation in early life as a potential pathway underlying PFAS-related health outcomes and underscore the need to further account for susceptibility windows and sex-dimorphic effects in future investigations.			●							-	1	B	A
1002	ヒト（内分泌系）	Wang, Zhanyun; Cousins, Ian T; Scheringer, Martin; Hungerbühler, Konrad	Fluorinated alternatives to long-chain per € fluoroalkyl carboxylic acids (PFCAs), perfluoroalkane sulfonic acids (PFSAs) and their potential precursors	2013	Environ Int. 2013 Oct;60:242-8. doi: 10.1016/j.envint.2013.08.021.	Since 2000 there has been an on-going industrial transition to replace long-chain perfluoroalkyl carboxylic acids(PFCAs), perfluoroalkane sulfonic acids (PFSAs) and their precursors. To date, information on these replacements including their chemical identities, however, has not been published or made easily accessible to the public, hampering risk assessment and management of these chemicals. Here we review information on fluorinated alternatives in the public domain. We identify over 20 fluorinated substances that are applied in [i] fluoropolymer manufacture, [ii] surface treatment of textile, leather and carpets, [iii] surface treatment of food contact materials,[iv] metal plating, [v] fire-fighting foams, and [vi] other commercial and consumer products.We summarize current knowledge on their environmental releases, persistence, and exposure of biota and humans. Based on the limited information available, it is unclear whether fluorinated alternatives are safe for humans and the environment.We identify three major data gaps that must be filled to perform meaningful risk assessments and recommend generation of the missing data through cooperation among all stakeholders (industry, regulators, academic scientists and the public).			●	●						-		C	C
1003	ヒト（内分泌系）	Wang, Zhanyun; Cousins, Ian T; Scheringer, Martin; Buck, Robert C; Hungerbühler, Konrad	Global emission inventories for C1 € 4–C14 perfluoroalkyl carboxylic acid (PFCA) homologues from 1951 to 2030, Part II: The remaining pieces of the puzzle	2014	Environ Int. 2014 Aug;69:166-76. doi: 10.1016/j.envint.2014.04.006. Epub 2014 May 24.	We identify eleven emission sources of perfluoroalkyl carboxylic acids (PFCAs) that have not been discussed in the past. These sources can be divided into three groups: [i] PFCAs released as ingredients or impurities, e.g., historical and current use of perfluorobutanoic acid (PFBA), perfluorohexanoic acid (PFHxA) and their derivatives; [ii] PFCAs formed as degradation products, e.g., atmospheric degradation of some hydrofluorocarbons (HFCs) and hydrofluoroethers (HFEs); and [iii] sources from which PFCAs are released as both impurities and degradation products, e.g., historical and current use of perfluorobutane sulfonyl fluoride (PBSF)- and perfluorohexane sulfonyl fluoride (PHxSF)-based products. Available information confirms that these sources were active in the past or are still active today, but due to a lack of information, it is not yet possible to quantify emissions from these sources. However, our review of the available information on these sources shows that some of the sources may have been significant in the past (e.g., the historical use of PFBA-, PFHxA-, PBSF- and PHxSF-based products), whereas others can be significant in the long-term (e.g., (bio)degradation of various side-chain fluorinated polymers where PFCA precursors are chemically bound to the backbone). In addition, we summarize critical knowledge and data gaps regarding these sources as a basis for future research.			●							-		C	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1004	ヒト（内分泌系）	Webster, Glenys M; Rauch, Stephen A; Marie, Nathalie Ste; Mattman, Andre; Lanphear, Bruce P; Venners, Scott A	Cross-Sectional Associations of Serum Perfluoroalkyl Acids and Thyroid Hormones in U	2016	Environ Health Perspect. 2016 Jul;124(7):935-42. doi: 10.1289/ehp.1409589. Epub 2015 Oct 30.	BACKGROUND: Perfluoroalkyl acids (PFASs) are suspected thyroid toxicants, but results from epidemiological studies are inconsistent. OBJECTIVES: We examined associations between serum PFASs and thyroid hormones (THs) in a representative, cross-sectional sample of U.S. adults. We hypothesized that people with high thyroid peroxidase antibodies and low iodine would be more susceptible to PFAS-induced thyroid disruption. METHODS: Our sample included 1,525 adults (≥ 18 years) from the 2007-2008 NHANES study with available serum PFASs and THs. We examined associations between four serum PFASs [perfluorohexane sulfonate (PFHxS), perfluorononanoate (PFNA), perfluorooctanoate (PFOA), and perfluorooctane sulfonate (PFOS)], and serum THs [free triiodothyronine (fT3), free thyroxine (fT4), fT3/fT4, thyroid-stimulating hormone (TSH), total T3 (TT3), and total T4 (TT4)] using multivariable linear regression. We stratified subjects into four groups by two indicators of thyroid "stress": thyroid peroxidase antibody (TPOAb ≥ 9 IU/mL) and iodine status (< 100 μg/L urine). RESULTS: Of 1,525 participants, 400 (26%) had low iodine only (T0I1), 87 (6%) had high TPOAb only (T1I0), and 26 (2%) had both high TPOAb and low iodine (T1I1). In general, associations were similar among participants in the groups with neither (T0I0) or only one thyroid stressor (T0I1 or T1I0), suggesting that PFAS-TH associations were not modified by high TPOAb or low iodine alone. However, PFHxS and PFOS were negatively associated (p < 0.05) with fT4, and all four PFASs were positively associated (p < 0.05) with fT3, fT3/fT4, TSH, and TT3 in the group with joint exposure to high TPOAb and low iodine (T1I1). CONCLUSIONS: We found evidence of PFAS-associated thyroid disruption in a subset of U.S. adults with high TPOAb (a marker of autoimmune hypothyroidism) and low iodine status, who may represent a vulnerable subgroup. However, the small sample size, cross-sectional design, and possibility of reverse causation are limitations of this work. CITATION: Webster GM, Rauch SA, Ste Marie N, Mattman A, Lanphear BP, Venners SA. 2016. Cross-sectional associations of serum perfluoroalkyl acids and thyroid hormones in U.S. adults: variation according to TPOAb and iodine status (NHANES 2007-2008).			●	●						-		B	B
1005	ヒト（内分泌系）	Dallaire, Renée; Ayotte, Pierre; Pereg, Daria; Déry, Serge; Dumas, Pierre; Langlois, Eric; Dewailly, Eric	Determinants of plasma concentrations of perfluorooctanesulfonate and brominated organic compounds in Nunavik Inuit adults (Canada)	2009	Environ Sci Technol. 2009 Jul 1;43(13):5130-6. doi: 10.1021/es9001604.	Perfluorooctanesulfonate (PFOS) and brominated organic compounds (BOCs) have been found in biota and humans worldwide with levels of BOCs being the highest in North America. PFOS and BOC exposure of remote populations that consume species of a marine food web for their subsistence has seldom been investigated. In 2004, we determined the concentrations of these contaminants in 883 Nunavik Inuit adults from the Canadian Arctic and investigated the demographic and dietary factors associated with them. Demographic and dietary information were collected by questionnaires. Multiple linear regressions were conducted to investigate predictors of exposure to those contaminants. Polychlorinated biphenyl (PCB) congener 153 concentrations are presented for comparative purposes. PFOS and PCB 153 were detected in all samples, with plasma concentrations several times higher than BOCs. The consumption of fish and marine mammals appears to be an important contributor to PFOS exposure among Nunavik Inuit. While PBDE 153 also appears as a persistent PBDE congener, exposure to PBDE 47 seems to be more recent in this population. Adoption of a westernized lifestyle seems to be related to an increased exposure to PBDE 47, but specific sources remain to be elucidated. In conclusion, we found that the remote geographical location and traditional lifestyle of the Nunavik Inuit population do not protect them against exposure to emerging POPs, particularly PFOS.				●						-		C	C
1006	ヒト（内分泌系）	Wang Y, Starling AP, Haug LS, et al.	Association between perfluoroalkyl substances and thyroid stimulating hormone among pregnant women: A cross-sectional study	2013	Environ Health. 2013 Sep 8;12(1):76. doi: 10.1186/1476-069X-12-76.	Background: Perfluoroalkyl substances (PFASs) are a group of highly persistent chemicals that are widespread contaminants in wildlife and humans. Exposure to PFAS affects thyroid homeostasis in experimental animals and possibly in humans. The objective of this study was to examine the association between plasma concentrations of PFASs and thyroid stimulating hormone (TSH) among pregnant women. Methods: A total of 903 pregnant women who enrolled in the Norwegian Mother and Child Cohort Study from 2003 to 2004 were studied. Concentrations of thirteen PFASs and TSH were measured in plasma samples collected around the 18th week of gestation. Linear regression models were used to evaluate associations between PFASs and TSH. Results: Among the thirteen PFASs, seven were detected in more than 60% of samples and perfluorooctane sulfonate (PFOS) had the highest concentrations (median, 12.8 ng/mL; inter-quartile range [IQR], 10.1 -16.5 ng/mL). The median TSH concentration was 3.5 (IQR, 2.4 - 4.8) μIU/mL. Pregnant women with higher PFOS had higher TSH levels. After adjustment, with each 1 ng/mL increase in PFOS concentration, there was a 0.8% (95% confidence interval: 0.1%, 1.6%) rise in TSH. The odds ratio of having an abnormally high TSH, however, was not increased, and other PFASs were unrelated to TSH. Conclusions: Our results suggest an association between PFOS and TSH in pregnant women that is small and may be of no clinical significance.				●						-		D	D
1007	ヒト（内分泌系）	Dallaire, Renée; Dewailly, Eric; Pereg, Daria; Dery, Serge; Ayotte, Pierre	Thyroid function and plasma concentrations of polyhalogenated compounds in Inuit adults	2009	Environ Health Perspect. 2009 Sep;117(9):1380-6. doi: 10.1289/ehp.0900633. Epub 2009 May 12.	BACKGROUND: Several ubiquitous polyhalogenated compounds (PHCs) have been shown to alter thyroid function in animal and in vitro studies. So far, epidemiologic studies have focused on the potential effect of a small number of them, namely, polychlorinated biphenyls (PCBs) and some organochlorines (OCs), without paying attention to other important PHCs. OBJECTIVES: We investigated the relationship between exposure to several PHCs and thyroid hormone homeostasis in Inuit adults from Nunavik. METHODS: We measured thyroid parameters [thyroid-stimulating-hormone (TSH), free thyroxine (fT(4)), total triiodothyronine (tT(3)), and thyroxine-binding globulin (TBG)] and concentrations of 41 contaminants, including PCBs and their metabolites, organochlorine pesticides (OCPs), polybrominated diphenyl ethers (PBDEs), perfluorooctanesulfonate (PFOS), and a measure of dioxin-like compounds, detected in plasma samples from Inuit adults (n = 623). RESULTS: We found negative associations between tT(3) concentrations and levels of 14 PCBs, 7 hydroxylated PCBs (HO-PCBs), all methylsulfonyl metabolites of PCBs (MeSO(2)-PCBs), and 2 OCPs. Moreover, we found negative associations between fT(4) levels and hexachlorobenzene concentrations. TBG concentrations were inversely related to 8 PCBs, 5 HO-PCBs, and 3 OCPs. Exposure to BDE-47 was positively related to tT (3), whereas PFOS concentrations were negatively associated with TSH, tT(3,) and TBG and positively with fT(4) concentrations. CONCLUSION: Exposure to several PHCs was associated with modifications of the thyroid parameters in adult Inuit, mainly by reducing tT(3) and TBG circulating concentrations. The effects of PFOS and BDE-47 on thyroid homeostasis require further investigation because other human populations display similar or higher concentrations of these chemicals.					●					-		C	C
1008	ヒト（内分泌系）	Olsen, G.W., Butenhoff, J.L. and Mandel, J.N.	Assessment of lipid, hepatic and thyroid function in relation to an occupational biologic limit value for perfluorooctanoate	2003	U.S. EPA AR226-1351.	No abstract available					●				US EPA docket を検索したが入手不可		D	D
1009	ヒト（内分泌系）	Olsen, G. W.; Burlew, M. M.; Burris, J. M.; Mandel, J. H.	A Cross-Sectional Analysis of Serum Perfluorooctane Sulfonate (PFOS) and Perfluorooctanoate (PFOA) in Relation to Clinical Chemistry, Thyroid Hormone, Hematology and Urinalysis Results from Male and Female Employee Participants of the 2000 Antwerp and Decatur Fluorochemical Medical Surveillance Program.	2001	Final Report. 3M Company, St. Paul, MN.	No abstract available							●		企業データ		D	D
1010	ヒト（内分泌系）	Gallo, Elisa; Barbiellini Amidei, Claudio; Barbieri, Giulia; Fabricio, Aline S C; Gion, Massimo; Pitter, Gisella; Daprà, Francesca; Russo, Francesca; Gregori, Dario; Fletcher, Tony; Canova, Cristina	Perfluoroalkyl substances and thyroid stimulating hormone levels in a highly exposed population in the Veneto Region	2022	Environ Res. 2022 Jan;203:111794. doi: 10.1016/j.envres.2021.111794. Epub 2021 Aug 3.	BACKGROUND: Per- and poly-fluoroalkyl substances (PFAS) are persistent and widespread environmental pollutants. People living in Veneto Region (Italy) have been exposed from the late 1970s to 2013 to elevated concentrations of PFAS through drinking water. The effect of PFAS on thyroid function is still controversial and studies focusing on thyroid stimulating hormone (TSH) have shown inconsistent results. The aim of this study was to evaluate the association between serum PFAS and TSH levels and its dose-response relationship in a large population of highly exposed individuals. METHODS: A cross-sectional study was conducted on 21,424 individuals aged 14-39 living in the contaminated area. In the main analysis, participants with prevalent thyroid disease and pregnant women were excluded. Serum levels of perfluorooctanoic acid (PFOA), perfluorooctanesulfonic acid (PFOS), perfluorohexanesulfonic acid (PFHxS) and perfluorononanoic acid (PFNA) were measured. Generalized Additive Models were used to evaluate the association between TSH levels and serum PFAS, using thin plate spline smooth terms to model the potential non-linear relationship. Models were stratified by sex and age group and adjusted for potential confounders. A secondary analysis was conducted to evaluate the association between PFAS with prevalent self-reported thyroid disorders. RESULTS: We found no association between TSH and any type of PFAS among adolescents or women. A decrease in TSH concentration was observed in association with an IQR increase in PFHxS and a mild decrease in TSH at low levels of PFOA, PFOS and PFHxS among male adults. Self-reported thyroid disease was more common among women with higher levels of PFNA concentrations, whereas all other PFAS were not associated with thyroid diseases regardless of sex or age. CONCLUSIONS: Overall there is no evidence of an association between TSH and PFAS. However, some results are suggestive of a possible inverse association of TSH with PFOA, PFOS and PFHxS among adult males.								●		-	1	B	A
1011	ヒト（神経毒性）	Berk, M.; Williams, L. J.; Andreazza, A. C.; Pasco, J. A.; Dodd, S.; Jacka, F. N.; Moylan, S.; Reiner, E. J.; Magalhaes, P. V. S.	Pop, heavy metal and the blues: secondary analysis of persistent organic pollutants (POP), heavy metals and depressive symptoms in the NHANES National Epidemiological Survey	2019	BMJ Open. 2014 Jul 18;4(7):e005142. doi: 10.1136/bmjopen-2014-005142.	Objectives: Persistent environmental pollutants, including heavy metals and persistent organic pollutants (POPs), have a ubiquitous presence. Many of these pollutants affect neurobiological processes, either accidentally or by design. The aim of this study was to explore the associations between assayed measures of POPs and heavy metals and depressive symptoms. We hypothesised that higher levels of pollutants and metals would be associated with depressive symptoms.	●	●	●							-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1012	ヒト（神経毒性）	Ding, N.; Park, S. K.	Perfluoroalkyl substances exposure and hearing impairment in US adults	2018	Environ Res. 2020 Aug;187:109686. doi: 10.1016/j.envres.2020.109686. Epub 2020 May 18.	BACKGROUND: Per- and polyfluoroalkyl substances (PFAS) are widely applied in consumer and industrial products such as nonstick cookware, waterproof clothing, food packaging materials, and fire-fighting foams. These "forever chemicals" are hypothesized to impact neurobehavioral functions. Yet no previous study has explored the role of PFAS on audiometrically determined hearing impairment (HI).OBJECTIVES: To investigate the associations of serum concentrations of perfluoroalkyl substances with low-frequency HI (LFHI) and high-frequency HI (HFHI) in US adults.METHODS: We evaluated the cross-sectional associations in 2371 adults aged 20-69 years who participated in the National Health and Nutrition Examination Survey (NHANES) 2003-2004, 2011-2012 and 2015-2016; and 449 adults aged ≥70 years from NHANES 2005-2006 and 2009-2010. Serum concentrations of perfluorohexane sulfonic acid (PFHxS), perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA) and perfluorodecanoic acid (PFDA), were measured using solid-phase extraction coupled to High Performance Liquid Chromatography-Turbo Ion Spray ionization-tandem Mass Spectrometry. LFHI was defined as a pure-tone average (PTA) of thresholds across 0.5-1-2 kHz >25 dB; HFHI defined as a PTA across 3-4-6 kHz >25 dB in the worse ear. Survey-weighted logistic regression models were used to compute odds ratios (ORs) and 0.95 confidence intervals (CIs) with adjustment for age, age-squared, sex, race/ethnicity, education, poverty-to-income ratio, body mass index, smoking status, exposures to occupational, recreational and firearm noises, and NHANES cycles.RESULTS: There were no significant associations when perfluoroalkyl variables were fitted as a linear (log-transformed) term. However, statistically significant associations of HFHI with PFNA (OR = 1.70, 0.95 CI: 1.13-2.56) and PFDA (OR = 1.75, 0.95 CI: 1.00-3.05) were observed when comparing participants with serum concentrations ≥90th vs. <90th percentiles of PFNA (90th percentile = 1.8 ng/mL) and PFDA (90th percentile = 0.5 ng/mL), respectively, in adults aged 20-69 years. No significant associations were observed for other compounds in adults aged 20-69 years and for all compounds in adults ≥70 years.CONCLUSIONS: Our study does not provide strong evidence to support the ototoxicity of PFAS exposure. Non-linear threshold dose-response associations between serum concentrations of PFNA and PFDA and HFHI need further investigation.	●	●							-		B	-
1013	ヒト（神経毒性）	Gallo, V.; Leonardi, G.; Brayne, C.; Armstrong, B.,en; Fletcher, T.	Serum perfluoroalkyl acids concentrations and memory impairment in a large cross-sectional study	2013	BMJ Open. 2013 Jun 20;3(6):e002414. doi: 10.1136/bmjopen-2012-002414.	Objectives: To examine the cross-sectional association between serum perfluorooctanate (PFOA), perfuorooctane sulfonate (PFOS), perfluorononanoic acid (PFNA) and perfluorohexane sulfonate (PFHxS) concentrations with self-reported memory impairment in adults and the interaction of these associations with diabetes status. Design: Cross-sectional study. Setting: Population-based in Mid-Ohio Valley, West Virginia following contamination by a chemical plant. Participants: The C8 Health Project collected data and measured the serum level of perfluoroalkyl acids (PFAAs) of 21 24 adults aged 50+ years. Primary outcome measure: Self-reported memory impairment as defined by the question have experienced short-term memory loss?' Results: A total of 4057 participants self-reported short-term memory impairment. Inverse associations between PFOS and PFOA and memory impairment were highly statistically significant with fully adjusted OR=0.93 (95% CI 0.9 to 0.96) for doubling PFOS and OR=0.96 (95% CI 0.94 to 0.98) for doubling PFOA concentrations. Comparable inverse associations with PFNA and PFHxS were of borderline statistical significance. Inverse associations of PFAAs with memory impairment were weaker or non-existent in patients with diabetes than overall in patients without diabetes. Conclusions: An inverse association between PFAA serum levels and self-reported memory impairment has been observed in this large population-based, cross-sectional study that is stronger and more statistically significant for PFOA and PFOS. The associations can be potentially explained by a preventive anti-inflammatory effect exerted by a peroxisome proliferator-activated receptor agonist effect of these PFAAs, but confounding or even reverse causation cannot be excluded as an alternative explanation.	●	●	●	●					-		B	-
1014	ヒト（発達神経毒性）	Ghassabian, A.; Bell, E. M.; Ma, W. L.; Sundaram, R.; Kannan, K.; Buck Louis, G. M.; Yeung, E.	Concentrations of perfluoroalkyl substances and bisphenol A in newborn dried blood spots and the association with child behavior	2018	Environ Pollut. 2018 Dec;243(Pt B):1629-1636. doi: 10.1016/j.envpol.2018.09.107. Epub 2018 Sep 27.	Experimental studies suggest that prenatal exposure to endocrine disrupting chemicals interferes with developmental processes in the fetal brain. Yet, epidemiological evidence is inconclusive. In a birth cohort (2008-2010, upstate New York), we quantified concentrations of perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), and bisphenol A (BPA) in stored newborn dried blood spots using liquid chromatography/tandem mass spectrometry. Mothers reported on children's behavior using the Strengths and Difficulties Questionnaire at age 7 (650 singletons and 138 twins). Difficulties in total behavior (i.e., emotional, conduct, hyperactivity, and peer problems) and prosocial behavior were classified using validated cut-offs. We used logistic regression with generalized estimating equations to estimate the odds of having difficulties per exposure category. In total, 111 children -0.121 had total behavioral difficulties and 60 -0.065 had difficulties in prosocial behavior. The median (interquartile range) of PFOS, PFOA, and BPA were 1.74 ng/ml (1.33), 1.12 ng/ml (0.96), and 7.93 ng/ml (10.79), respectively. Higher PFOS levels were associated with increased odds of having behavioral difficulties (OR per SD of log PFOS = 1.30, 95%CI: 1.03-1.65). We observed associations between PFOS in the highest relative to the lowest quartile and behavioral difficulties (OR for PFOS1.14-1.74 = 1.65, 95%CI: 0.84-3.34; PFOS1.75-2.47 = 1.73, 95%CI: 0.87-3.43; and PFOS>2.47 = 2.47, 95%CI: 1.29-4.72 compared to PFOS<1.41). The associations between higher concentrations of PFOS and behavioral difficulties at age 7 years were driven by problems in conduct and emotional symptoms. Higher PFOA levels were associated with difficulties in prosocial behavior (OR = 1.35, 95%CI: 1.03-1.75). There was an inverse association between BPA concentrations and difficulties in prosocial behavior but only in the 2nd and 4th quartiles. We found no interactions between sex and chemical concentrations. Increasing prenatal exposure to PFOS and PFOA, as reflected in neonatal concentrations, may pose risk for child behavioral difficulties.	●	●							-	1	A	-
1015	ヒト（発達神経毒性）	Harris, M. H.; Oken, E.; Rifas-Shiman, S. L.; Calafat, A. M.; Ye, X.; Bellinger, D. C.; Webster, T. F.; White, R. F.; Sagiv, S. K.	Prenatal and childhood exposure to per- and polyfluoroalkyl substances (PFASs) and child cognition	2018	Environ Int. 2018 Jun;115:358-369. doi: 10.1016/j.envint.2018.03.025. Epub 2018 Apr 26.	BACKGROUND: Per- and polyfluoroalkyl substances (PFASs) are suspected developmental toxicants, but epidemiological evidence on neurodevelopmental effects of PFAS exposure is inconsistent. We examined associations of prenatal and childhood PFAS exposure with performance on assessments of cognition in children.METHODS: We included mother-child pairs from Project Viva, a longitudinal Boston-area birth cohort enrolled during 1999-2002. We quantified concentrations of eight PFASs, including perfluorooctane sulfonate (PFOS), perfluorooctanoate (PFOA), and perfluorohexane sulfonate (PFHxS), in plasma collected from women during pregnancy (median 9.7 weeks gestation) and from children at a visit in mid-childhood (median age 7.7 years). In early childhood (median age 3.2 years) we administered standardized assessments of visual motor skills and vocabulary comprehension, and in mid-childhood we assessed visual motor skills, visual memory, and verbal and non-verbal intelligence. Using multivariable regression, we estimated associations of prenatal and childhood PFAS plasma concentrations with children's cognitive assessment scores, adjusted for relevant covariates including breastfeeding, maternal intelligence, parental education, and household income. Samples sizes ranged from 631 to 971, depending on analysis.RESULTS: Prenatal PFAS concentrations were associated with both better and worse cognitive performance; children with top quartile prenatal concentrations of some PFASs had better visual motor abilities in early childhood and non-verbal IQ and visual memory in mid-childhood, while children with upper quartile prenatal PFOA and PFOS had lower mid-childhood visual-motor scores. In cross-sectional analyses of mid-childhood PFAS concentrations and cognitive assessments, visual-motor scores on the Wide Range Assessment of Visual Motor Abilities (WRAVMA) (standardized mean = 100, standard deviation = 15) were lower among children with higher PFHxS (fourth quartile (Q4) vs. Q1: -5.0, 0.95 confidence interval (CI): -9.1, -0.8). Upper quartiles of childhood PFOA and PFOS were also associated with somewhat lower childhood WRAVMA scores, but childhood PFASs were not associated with verbal or non-verbal IQ or visual memory.CONCLUSIONS: We present evidence suggesting associations of prenatal and childhood PFAS exposure with lower childhood visual motor abilities. Other results were inconsistent, with higher prenatal PFASs associated in some cases with better cognitive outcomes.	●	●							-	1	A	-
1016	ヒト（発達神経毒性）	Lenters, V.; Iszatt, N.; Forns, J.; Čechová, E.; Kočan, A.; Legler, J.; Leonards, P.; Stigum, H.; Eggesbø, M.	Early-life exposure to persistent organic pollutants (OCPs, PBDEs, PCBs, PFASs) and attention-deficit/hyperactivity disorder: A multi-pollutant analysis of a Norwegian birth cohort	2019	Environ Int. 2019 Apr;125:33-42. doi: 10.1016/j.envint.2019.01.020. Epub 2019 Jan 28.	BACKGROUND: Numerous ubiquitous environmental chemicals are established or suspected neurotoxicants, and infants are exposed to a mixture of these during the critical period of brain maturation. However, evidence for associations with the risk of attention-deficit/hyperactivity disorder (ADHD) is sparse. We investigated early-life chemical exposures in relation to ADHD.METHODS: We used a birth cohort of 2606 Norwegian mother-child pairs enrolled 2002-2009 (HUMIS), and studied a subset of 1199 pairs oversampled for child neurodevelopmental outcomes. Concentrations of 27 persistent organic pollutants (14 polychlorinated biphenyls, 5 organochlorine pesticides, 6 brominated flame retardants, and 2 perfluoroalkyl substances) were measured in breast milk, reflecting the child's early-life exposures. We estimated postnatal exposures in the first 2 years of life using a pharmacokinetic model. Fifty-five children had a clinical diagnosis of ADHD (hyperkinetic disorder) by 2016, at a median age of 13 years. We used elastic net penalized logistic regression models to identify associations while adjusting for co-exposure confounding, and subsequently used multivariable logistic regression models to obtain effect estimates for the selected exposures.RESULTS: Breast milk concentrations of perfluorooctane sulfonate (PFOS) and β-hexachlorocyclohexane (β-HCH) were associated with increased odds of ADHD: odds ratio (OR) = 1.77, 0.95 confidence interval (CI): 1.16, 2.72 and OR = 1.75, 0.95 CI: 1.22, 2.53, per interquartile range increase in ln-transformed concentrations, respectively. Stronger associations were observed among girls than boys for PFOS (pinteraction = 0.025). p,p'-Dichlorodiphenyltrichloroethane (p,p'-DDT) levels were associated with lower odds of ADHD (OR = 0.64, 0.95 CI: 0.42, 0.97). Hexachlorobenzene (HCB) had a non-linear association with ADHD, with increasing risk in the low-level exposure range that switched to a decreasing risk at concentrations above 8 ng/g lipid. Postnatal exposures showed similar results, whereas effect estimates for other chemicals were weaker and imprecise.CONCLUSIONS: In a multi-pollutant analysis of four classes of chemicals, early-life exposure to β-HCH and PFOS was associated with increased risk of ADHD, with suggestion of sex-specific effects for PFOS. The unexpected inverse associations between p,p'-DDT and higher HCB levels and ADHD could be due to live birth bias; alternatively, results may be due to chance findings.	●								-	1	A	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1017	ヒト（神経毒性）	Li, M. C.	Transplacental Transfer of Per- and Polyfluoroalkyl Substances Identified in Paired Maternal and Cord Sera Using Suspect and Nontarget Screening	2020	Int J Environ Res Public Health. 2020 Aug 12;17(16):5836. doi: 10.3390/ijerph17165836.	Although studies have shown that per- and polyfluoroalkyl substances (PFAS) are potential environmental ototoxicants, epidemiologic study has been limited. I conducted a cross-sectional study to re-examine the associations between PFAS and hearing impairment. Data were obtained from the National Health and Nutrition Examination Survey (NHANES) 1999-2000, 2003-06, 2009-12, and 2015-16. Perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorohexane sulfonic acid (PFHxS), and perfluorononanoic acid (PFNA) were measured in serum samples. Participants were divided into quartiles for each PFAS. Air conduction pure-tone audiometry was administered. Hearing impairment (1: yes, 0 no) was defined as a hearing threshold of more than 25 dB at 500, 1000, 2000, 4000, and 8000 Hz in the worse ear. I assessed the relation of serum PFAS with hearing impairment by the generalized linear mixed model with a logit link and binary distribution. Tests for linear trend across quartiles of serum PFAS were conducted using the median serum PFAS in each quartile as a continuous variable. After adjusting for age, sex, body mass index, education, ethnicity group, and family income, I found positive correlations between PFOA and hearing impairment at 2000 Hz (p-trend < 0.01) and 3000 Hz (p-trend = 0.02); between PFOS and hearing impairment at 500 Hz (p-trend < 0.01), 2000 Hz (p-trend < 0.0001) and 3000 Hz (p-trend = 0.02); between PFNA and hearing impairment at 2000 Hz (p-trend = 0.05), 3000 Hz (p-trend < 0.01), 4000 Hz (p-trend = 0.02), and 8000 Hz (p-trend < 0.01); between PFHxS and hearing impairment at 500 Hz (p-trend = 0.04), 1000 Hz (p-trend = 0.03), and 2000 Hz (p-trend < 0.01). However, some of the findings were not significant when only comparing the highest with the lowest quartile of PFASs. In conclusion, several background serum PFASs are positively correlated with hearing impairment in the United States adult population.	●	●							-		C	-
1018	ヒト（神経毒性）	Liew, Z.; Ritz, B.; Bach, C. C.; Asarnow, R. F.; Bech, B. H.; Nohr, E. A.; Bossi, R.; Henriksen, T. B.; Bonefeld-Jørgensen, E. C.; Olsen, J.	Prenatal exposure to perfluoroalkyl substances and iq scores at age 5; a study in the danish national birth cohort	2018	Environ Health Perspect. 2018 Jun 12;126(6):067004. doi: 10.1289/EHP2754. eCollection 2018 Jun.	BACKGROUND: Perfluoroalkyl substances (PFASs) are widespread persistent organic compounds that have been suggested to affect neurodevelopment.OBJECTIVE: We aimed to evaluate whether prenatal exposure to PFASs is associated with IQ in children.METHODS: We studied 1592 pregnancies enrolled in the Danish National Birth Cohort (DNBC) during 1996-2002. Sixteen PFASs were measured in maternal plasma collected in early gestation. Child IQ was assessed at 5 y of age using the Wechsler Primary and Preschool Scales of Intelligence-Revised (WPPSI-R) administered by trained psychologists. Using multivariable linear regression models, we estimated the differences in child IQ scores according to PFAS concentration [per natural-log (ng/mL) unit increase or values categorized in quartiles].RESULTS: Perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) were detected in all samples, and five additional PFASs were quantified in >80% of the samples. Overall, we found no strong associations between a natural-log unit increase in each of the seven PFASs we evaluated and child IQ scores. A few positive and negative associations were found in the sex-stratified PFAS quartile analyses, but the patterns were inconsistent.CONCLUSION: Overall, we did not find consistent evidence to suggest prenatal exposure to PFASs to be associated with child IQ scores at 5 y of age in the DNBC. Some of the sex-specific observations warrant further investigation. Additional studies should examine offspring IQ at older ages and assess other functional cognitive and neuropsychiatric measures in addition to intelligence. Postnatal exposures to PFASs and mixture effects for PFASs and PFASs with other environmental pollutants should also be considered in future research.	●	●							-		B	-
1019	ヒト（神経毒性）	Long, M.; Ghisari, M.; Kjeldsen, L.; Wielsøe, M.; Nørgaard-Pedersen, B.; Mortensen, E. L.; Abdallah, M. W.; Bonefeld-Jørgensen, E. C.	Autism spectrum disorders, endocrine disrupting compounds, and heavy metals in amniotic fluid: a case-control study	2019	Mol Autism. 2019 Jan 9;10:1. doi: 10.1186/s13229-018-0253-1. eCollection 2019.	Background: Evidence has indicated that some non-inherited factors such as exposure to environmental pollutants are associated with neurodevelopment disorders like autism spectrum disorder (ASD). Studies report that endocrine disrupting compounds (EDCs), including polychlorinated biphenyls, organochlorine pesticides, perfluoroalkyl substances (PFAS), and some metals, have adverse effects on the fetal neurodevelopment. The aim of this study was to measure the amniotic fluid (AF) levels of EDCs and metals as well as the receptor transactivities induced by AF and investigate the possible link between prenatal exposure to EDCs and heavy metals and ASD risk.Methods: In this case-control study, we included AF samples of 75 ASD cases and 135 frequency-matched controls and measured the levels of the endogenous sex hormones, PFAS, and elements including heavy metals. The combined effect of endogenous hormones and EDCs on the receptor of estrogen (ER), androgen (AR), aryl hydrocarbon (AhR), and thyroid hormone-like activity were also determined and expressed as receptor ligand equivalents. We assessed the associations of AF levels of chemicals, sex hormones, and receptor activities with ASD risk using unconditional logistical regression analyses. To control for multiple comparisons, the FALSE discovery rate (FDR) was used and q values less than 0.25 were designated as statistical significance.Results: PFAS and metals were detectable in AF samples. The ASD cases had significantly lower AF levels of PFAS than controls, and the adjusted odds ratio (OR) was 0.41 (95% CI 0.174, 0.967; p = 0.042; FDR qvalue = 0.437) for perfluorooctane sulfonate (PFOS). The principal component, including PFAS congeners, copper, iron, and estrogenic activity, was significantly inversely associated with ASD risk (adjusted OR = 0.100; 0.95 CI 0.016, 0.630; p = 0.014; FDR qvalue = 0.098).Testosterone level in AF weakly associated with ASD risk (adjusted OR = 1.002; 0.95 CI 1.000, 1.004; p = 0.05). However, after multiple comparison correction, the association was not significant (FDR qvalue = 0.437). No significant associations between AF-induced receptor transactivities and ASD risk were observed. The adjusted OR was 2.176 (95%CI 0.115, 41.153) for the ratio of the combined androgenic activity to combined estrogenic activity.Conclusions: The presence of PFAS and heavy metals in AF indicates that they can cross the placenta. The inverse association between levels of PFAS congeners in AF and ASD risk might relate to the weak estrogenic activities and anti-androgenic activities of PFAS.The observed tendency of positive association between the ratio of combined androgenic effect to the combined estrogenic effect and ASD risk needs further studies to explore whether EDCs together with	●	●	●						-		B	-
1020	ヒト（神経毒性）	Lyall, K.; Yau, V. M.; Hansen, R.; Kharrazi, M.; Yoshida, C. K.; Calafat, A. M.; Windham, G.; Croen, L. A.	Prenatal maternal serum concentrations of per- and polyfluoroalkyl substances in association with autism spectrum disorder and intellectual disability	2018	Environ Health Perspect. 2018 Jan 2;126(1):017001. doi: 10.1289/EHP1830.	BACKGROUND: Emerging work has examined neurodevelopmental outcomes following prenatal exposure to per- and polyfluoroalkyl substances (PFAS), but few studies have assessed associations with autism spectrum disorder (ASD).OBJECTIVES: Our objective was to estimate associations of maternal prenatal PFAS concentrations with ASD and intellectual disability (ID) in children.METHODS: Participants were from a population-based nested case-control study of children born from 2000 to 2003 in southern California, including children diagnosed with ASD (n=553), ID without autism (n=189), and general population (GP) controls (n=433). Concentrations of eight PFAS from stored maternal sera collected at 15-19 wk gestational age were quantified and compared among study groups. We used logistic regression to obtain adjusted odds ratios for the association between prenatal PFAS concentrations (parameterized continuously and as quartiles) and ASD versus GP controls, and separately for ID versus GP controls.RESULTS: Geometric mean concentrations of most PFAS were lower in ASD and ID groups relative to GP controls. ASD was not significantly associated with prenatal concentrations of most PFAS, though significant inverse associations were found for perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) [adjusted ORs for the highest vs. lowest quartiles 0.62 (95% CI: 0.41, 0.93) and 0.64 (95% CI: 0.43, 0.97), respectively]. Results for ID were similar.CONCLUSIONS: Results from this large case-control study with prospectively collected prenatal measurements do not support the hypothesis that prenatal exposure to PFAS is positively associated with ASD or ID.	●	●							-		B	-
1021	ヒト（神経毒性）	Niu, J.; Liang, H.; Tian, Y.; Yuan, W.; Xiao, H.; Hu, H.; Sun, X.; Song, X.; Wen, S.; Yang, L.; Ren, Y.; Miao, M.	Prenatal plasma concentrations of Perfluoroalkyl and polyfluoroalkyl substances and neuropsychological development in children at four years of age	2019	Environ Health. 2019 Jun 13;18(1):53. doi: 10.1186/s12940-019-0493-3.	OBJECTIVE: Perfluoroalkyl and polyfluoroalkyl substances (PFASs) are persistent pollutants and have endocrine disruptive and neurotoxic effects. The association between maternal PFAS concentrations and neuropsychological development in children is inconclusive. The present study aimed to examine the effect of maternal PFAS concentrations on neuropsychological development in 4-years-old children.METHODS: We used data from Shanghai-Minhang Birth Cohort, which recruited pregnant women at 44911 gestational weeks. Among 981 women having PFAS measurement, 533 mother-child pairs were included in the study. A total of eight PFASs were measured, including perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), perfluorohexane sulfonate (PFHxS), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUdA), perfluorododecanoic acid (PFDoA), and perfluorotridecanoic acid (PFTrDA). When infants turned 4 years old, mothers were asked to complete the Ages and Stages Questionnaires® (ASQ) to assess neuropsychological development of their children. Poisson regression model with robust variance estimates was used to examine the association between maternal PFAS concentrations and each developmental subscale of the ASQ.RESULTS: Prenatal plasma concentrations of most PFASs tended to be associated with increased risk of development problem in personal-social skills, including PFHxS, PFOS, PFOA, PFNA, PFDA, and PDUdA, and the associations for PFNA and PFDA were significant (per natural log unit increase: RRPFNA = 1.92, 0.95 CI: 1.21, 3.05; RR PFDA = 1.66, 0.95 CI: 1.17, 2.37). In stratified analyses by child' sex, the consistent pattern of higher risk of developmental problems in personal-social skills associated with most PFASs was mainly observed among girls (RRPFOS = 2.56, 0.95 CI: 1.20, 5.45; RRPFOA = 9.00, 0.95 CI: 3.82, 21.21; RRPFNA = 3.11, 0.95 CI: 1.36, 7.13; RRPFDA = 2.20, 0.95 CI: 1.21, 4.00; RRPFUdA = 2.44, 0.95 CI: 1.14, 5.20; RRPFDoA = 1.62, 0.95 CI: 1.04, 2.54). Boys with higher maternal PFOA concentrations had a decreased risk of developmental problems in gross motor skills (RR = 0.47, 0.95 CI: 0.25, 0.89).CONCLUSION: Prenatal plasma PFAS concentrations were associated with neuropsychological development in girls at 4 years of age, mainly in the subset of personal-social skills.	●	●							-		B	-
1022	ヒト（神経毒性）	Oulhote, Y.; Coull, B.; Bind, M. A.; Debes, F.; Nielsen, F.; Tamayo, I.; Weihe, P.; Grandjean, P.	Joint and independent neurotoxic effects of early life exposures to a chemical mixture: A multi-pollutant approach combining ensemble learning and g-computation	2019	Environ Epidemiol. 2019 Oct;3(5):e063. doi: 10.1097/ee9.0000000000000063.	Background: Exposure to mercury (Hg) is associated with adverse developmental effects. However, Hg occurs with a multitude of chemicals. We assessed the associations of developmental exposure to multiple pollutants with children's neurodevelopment using a novel approach.	●	●							-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ランク①	文献ランク②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1023	ヒト（神経毒性）	Piekarski, D J; Diaz, K R; McNerney, M W	Perfluoroalkyl chemicals in neurological health and disease: Human concerns and animal models [Review]	2020	Neurotoxicology. 2020 Mar;77:155-168. doi: 10.1016/j.neuro.2020.01.001. Epub 2020 Jan 18.	Perfluoroalkyl acids (PFAAs) are man-made organic pollutants that are found ubiquitously in the environment and may impact human health. Here, we review the published literature concerning PFAA impacts on neurobiological, neuroendocrine, and neurobehavioral outcomes. We find that there are many mechanisms through which PFAAs may enter the brain and interact with biochemical endpoints to impact neurological function. These results are supported by epidemiological evidence in humans and experimental evidence in animals that demonstrate numerous and varied PFAA impacts on the nervous system. However, the methods commonly used in animal models of PFAA exposure result in durations of exposure and serum PFAA concentrations in blood that may not appropriately mimic human absorption, distribution, metabolism, and excretion. If animal models lack validity, confidence in mechanistic inferences regarding PFAA exposure and brain function is reduced, limiting these studies' utility. Finally, we end by suggesting some potential impacts of PFAA exposure in human neurological health and disease states whose associations may not readily present themselves in the epidemiological literature.	●	●							レビュー		A	-
1024	ヒト（神経毒性）	Shin, H. M.; Bennett, D. H.; Calafat, A. M.; Tancredi, D.; Hertz-Picciotto, I.	Modeled prenatal exposure to per- and polyfluoroalkyl substances in association with child autism spectrum disorder: A case-control study	2020	Environ Res. 2020 Jul;186:109514. doi: 10.1016/j.envres.2020.109514. Epub 2020 Apr 14.	BACKGROUND/OBJECTIVE: Per- and polyfluoroalkyl substances (PFAS) display neurobehavioral toxicity in laboratory animal studies. We examined associations of modeled prenatal maternal exposure to PFAS with child diagnosis of autism spectrum disorder (ASD).METHODS: Participants were 453 mother-child pairs from CHARGE (CHildhood Autism Risk from Genetics and Environment), a population-based case-control study. Children underwent psychometric testing and were clinically confirmed for ASD (n = 239) or typical development (TD, n = 214). At the end of the clinic visit, maternal blood specimens were collected. We quantified nine PFAS in maternal serum samples collected when their child was 44597 years old. As surrogate in utero exposure, we used a model built from external prospective data in pregnancy and 24 months post-partum and then reconstructed maternal PFAS serum concentrations during pregnancy in this case-control sample. We used logistic regression to evaluate associations of modeled prenatal maternal PFAS concentrations with child ASD.RESULTS: Modeled prenatal maternal perfluorohexane sulfonate (PFHxS) and perfluorooctane sulfonate (PFOS) were borderline associated with increased odds of child diagnosis of ASD (per nanogram per milliliter increase: odds ratio [OR] = 1.46; 0.95 confidence interval [CI]: 0.98, 2.18 for PFHxS, OR = 1.03; 0.95 CI: 0.99, 1.08 for PFOS). When compared to the lowest quartile (reference category), the highest quartile of modeled prenatal maternal PFHxS was associated with increased odds of child diagnosis of ASD (OR = 1.95; 0.95 CI: 1.02, 3.72).CONCLUSIONS: In analyses where modeled prenatal maternal PFAS serum concentrations served as in utero exposure, we observed that prenatal PFHxS and PFOS exposure, but not other PFAS, were borderline associated with increased odds of child diagnosis of ASD. Further studies in which PFAS concentrations are prospectively measured in mothers and children at a range of developmental stages are needed to confirm these findings.	●	●							-		B	-
1025	ヒト（神経毒性）	Shrestha, S.; Bloom, M. S.; Yucel, R.; Seegal, R. F.; Rej, R.; Mccaffrey, R. J.; Wu, Q.; Kannan, K.; Fitzgerald, E. F.	Perfluoroalkyl substances, thyroid hormones, and neuropsychological status in older adults	2017	Int J Hyg Environ Health. 2017 Jun;220(4):679-685. doi: 10.1016/j.ijheh.2016.12.013. Epub 2016 Dec 30.	Minimal data exist regarding the neurotoxicity of perfluoroalkyl substances (PFASs) in aging populations and the possible mediating effects of thyroid hormones (THs). Hence, the aims of this study were to: (i) assess associations between PFASs and neuropsychological function, and (ii) determine if such associations are mediated by changes in circulating THs in an aging population. We measured perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), total thyroxine (T4) and free thyroxine (fT4) in serum and performed neuropsychological tests in 126 men and women aged 55-74 years and living in upper Hudson River communities. Multivariable linear regressions were conducted to assess associations between PFASs and neuropsychological test scores. Mediation analyses were performed in a subset of 87 participants for whom information was available on both PFASs and THs. We calculated TH-mediated, non-TH mediated, and total effects of PFASs on neuropsychological test scores. Higher PFOA was associated with better performance in tasks of the California Verbal Learning Test and the Wisconsin Card Sorting Test. Higher PFOS was associated with improved performance in a Wechsler Memory Scale subtest and Block Design Subtest (BDT) total scores. There was no evidence of mediation by THs for PFOA-neuropsychological function associations. However, T4 and fT4 partially mediated the protective effect of PFOS on BDT total scores. Our findings do not suggest that PFASs are associated with poor neuropsychological function. There was some evidence of mediation for the association between PFASs and neuropsychological functions by THs, although some other modes of action also appear likely.	●	●		●					-		B	-
1026	ヒト（神経毒性）	Skogheim, T. S.; Villanger, G. D.; Weyde, K. V. F.; Engel, S. M.; Surén, P.; Øie, M. G.; Skogan, A. H.; Biele, G.; Zeiner, P.; Øvergaard, K. R.; Haug, L. S.; Sabaredzovic, A.; Aase, H.	Prenatal exposure to perfluoroalkyl substances and associations with symptoms of attention-deficit/hyperactivity disorder and cognitive functions in preschool children	2019	Int J Hyg Environ Health. 2020 Jan;223(1):80-92. doi: 10.1016/j.ijheh.2019.10.003. Epub 2019 Oct 22.	BACKGROUND: Perfluoroalkyl substances (PFASs) are persistent organic pollutants that are suspected to be neurodevelopmental toxicants, but epidemiological evidence on neurodevelopmental effects of PFAS exposure is inconsistent. We investigated the associations between prenatal exposure to PFASs and symptoms of attention-deficit/hyperactivity disorder (ADHD) and cognitive functioning (language skills, estimated IQ and working memory) in preschool children, as well as effect modification by child sex.MATERIAL AND METHODS: This study included 944 mother-child pairs enrolled in a longitudinal prospective study of ADHD symptoms (the ADHD Study), with participants recruited from The Norwegian Mother, Father and Child Cohort Study (MoBa). Boys and girls aged three and a half years, participated in extensive clinical assessments using well-validated tools; The Preschool Age Psychiatric Assessment interview, Child Development Inventory and Stanford-Binet (5th revision). Prenatal levels of 19 PFASs were measured in maternal blood at week 17 of gestation. Multivariable adjusted regression models were used to examine exposure-outcome associations with two principal components extracted from the seven detected PFASs. Based on these results, we performed regression analyses of individual PFASs categorized into quintiles.RESULTS: PFAS component 1 was mainly explained by perfluoroheptane sulfonate (PFHpS), perfluorooctane sulfonate (PFOS), perfluorohexane sulfonate (PFHxS) and perfluorooctanoic acid (PFOA). PFAS component 2 was mainly explained by perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA) and perfluorononanoic acid (PFNA). Regression models showed a negative association between PFAS component 1 and nonverbal working memory [β = -0.08 (CI: -0.12, -0.03)] and a positive association between PFAS component 2 and verbal working memory [β = 0.07 (CI: 0.01, 0.12)]. There were no associations with ADHD symptoms, language skills or IQ. For verbal working memory and PFAS component 2, we found evidence for effect modification by child sex, with associations only for boys. The results of quintile models with individual PFASs, showed the same pattern for working memory as the results in the component regression analyses. There were negative associations between nonverbal working memory and quintiles of PFOA, PFNA, PFHxS, PFHpS and PFOS and positive associations between verbal working memory and quintiles of PFOA, PFNA, PFDA and PFUnDA, with significant relationships mainly in the highest concentration groups.CONCLUSIONS: Based on our results, we did not find consistent evidence to conclude that prenatal exposure to PFASs are associated with ADHD symptoms or cognitive dysfunctions in preschool children aged three and a half years, which is in line with the majority of studies in this area. Our results showed some associations between 2 was mainly explained by perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA) and perfluorononanoic acid (PFNA). Regression models showed a negative association between PFAS component 1 and nonverbal working memory [β = -0.08 (CI: -0.12, -0.03)] and a positive association between PFAS component 2 and verbal working memory [β = 0.07 (CI: 0.01, 0.12)]. There were no associations with ADHD symptoms, language skills or IQ. For verbal working memory and PFAS component 2, we found evidence for effect modification by child sex, with associations only for boys. The results of quintile models with individual PFASs, showed the same pattern for working memory as the results in the component regression analyses. There were negative associations between nonverbal working memory and quintiles of PFOA, PFNA, PFHxS, PFHpS and PFOS and positive associations between verbal working memory and quintiles of PFOA, PFNA, PFDA and PFUnDA, with significant relationships mainly in the highest concentration groups.CONCLUSIONS: Based on our results, we did not find consistent evidence to conclude that prenatal exposure to PFASs are associated with ADHD symptoms or cognitive dysfunctions in preschool children aged	●	●							-		B	-
1027	ヒト（発達神経毒性）	Spratlen, M. J.; Perera, F. P.; Lederman, S. A.; Rauh, V. A.; Robinson, M.; Kannan, K.; Trasande, L.; Herbstman, J.	The association between prenatal exposure to perfluoroalkyl substances and childhood neurodevelopment	2020	Environ Pollut. 2020 Aug;263(Pt B):114444. doi: 10.1016/j.envpol.2020.114444. Epub 2020 Mar 26.	Perfluoroalkyl substances (PFAS) were among various persistent organic pollutants suspected to have been released during the collapse of the World Trade Center (WTC) on 9/11. Evidence on the association between prenatal PFAS exposure and child neurodevelopment is limited and inconsistent. This study evaluated the association between prenatal PFAS exposure and child cognitive outcomes measured at 5 different time points in a population prenatally exposed to the WTC disaster. The study population included 302 pregnant women in the Columbia University WTC birth cohort enrolled between December 13, 2001 and June 26, 2002 at three hospitals located near the WTC site: Beth Israel, St. Vincent's, and New York University Downtown. We evaluated the association between prenatal exposure to four PFAS (perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), perfluorohexanesulfonic acid (PFHxS), perfluorononanoic acid (PFNA)) and child neurodevelopment measured using the Bayley Scales of Infant Development (BSID-II) at approximately 1, 2 and 3 years of age and using The Wechsler Preschool and Primary Scale of Intelligence (WPPSI) at approximately 4 and 6 years of age. Geometric mean (range) concentrations of PFAS were 6.03 (1.05, 33.7), 2.31 (0.18, 8.14), 0.43 (<LOQ, 10.3) and 0.67 (<LOQ, 15.8) ng/mL for PFOS, PFOA, PFNA and PFHxS, respectively. Several PFAS were associated with increases in cognitive outcomes in females and overall (males and females combined). Child sex modified the association between PFOS and the mental development index measured using BSID-II, with the observed relationship being positive for females and negative for males. Through principal component analyses, we observed a negative relationship between PFNA and the psychomotor development index measured using BSID-II and the verbal IQ measured using WPPSI. Our results suggest a sex- and compound-specific relationship between prenatal PFAS exposures and childhood neurodevelopment.	●	●							-	1	A	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①情報抽出	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1028	ヒト（神経毒性）	Vuong, A. M.; Braun, J. M.; Yolton, K.; Wang, Z.; Xie, C.; Webster, G. M.; Ye, X.; Calafat, A. M.; Dietrich, K. N.; Lanphear, B. P.; Chen, A.	Prenatal and childhood exposure to perfluoroalkyl substances (PFAS) and measures of attention, impulse control, and visual spatial abilities	2018	Environ Int. 2018 Oct;119:413-420. doi: 10.1016/j.envint.2018.07.013. Epub 2018 Jul 20.	BACKGROUND: Despite evidence from toxicological studies describing the potential neurotoxicity of perfluoroalkyl substances (PFAS), their role in neurodevelopment remains uncertain amid inconsistent findings from epidemiological studies.METHODS: Using data from 218 mother-child dyads from the Health Outcomes and Measures of the Environment Study, we examined prenatal and childhood (3 and 8 years) serum concentrations of four PFAS and inattention, impulsivity, and visual spatial abilities. At 8 years, we used the Conners' Continuous Performance Test-II to assess attention and impulse control and the Virtual Morris Water Maze (VMWM) to measure visual spatial abilities.RESULTS: In multiple informant models, there was no evidence to indicate that prenatal or childhood PFAS are associated with attention. However, there was an inverse association between prenatal ln-perfluorooctanoate (PFOA) and errors of commission (β = -2.0, 0.95 Confidence Interval [CI] -3.8, -0.3). Ln-perfluorononanoate (PFNA) at 3 years was associated with longer (poorer) VMWM completion times of 3.6 seconds (CI 1.6, 5.6). However, higher concurrent concentrations of ln-perfluorohexane sulfonate (PFHxS) (β = -2.4 s, 0.95 CI -4.4, -0.3) were associated with shorter (better) times. Higher prenatal PFHxS was positively associated with percentage of traveling distance in the correct quadrant (β = 4.2%, 0.95 CI 0.8, 7.7), indicating better performance.CONCLUSION: Findings were mixed for prenatal and childhood PFAS concentrations and visual spatial abilities. There is not enough evidence to support that PFAS are associated with visual spatial abilities as assessed by the VMWM or CPT-II measures of inattention or impulsivity in children at age 8 years.	●	●							-		B	-
1029	ヒト（神経毒性）	Vuong, A. M.; Xie, C.; Jandarov, R.; Dietrich, K. N.; Zhang, H.; Sjödin, A.; Calafat, A. M.; Lanphear, B. P.; Mccandless, L.; Braun, J. M.; Yolton, K.; Chen, A.	Prenatal exposure to a mixture of persistent organic pollutants (POPs) and child reading skills at school age	2020	Int J Hyg Environ Health. 2020 Jul;228:113527. doi: 10.1016/j.ijheh.2020.113527. Epub 2020 Jun 7.	Prenatal exposure to persistent organic pollutants (POPs) may affect child neurobehavior; however, exposures to mixtures of POPs have rarely been examined.	●	●							-		B	-
1030	ヒト（神経毒性）	Vuong, A. M.; Yolton, K.; Braun, J. M.; Sjodin, A.; Calafat, A. M.; Xu, Y.; Dietrich, K. N.; Lanphear, B. P.; Chen, A.	Polybrominated diphenyl ether (PBDE) and poly- and perfluoroalkyl substance (PFAS) exposures during pregnancy and maternal depression	2020	Environ Int. 2020 Jun;139:105694. doi: 10.1016/j.envint.2020.105694. Epub 2020 Apr 5.	BACKGROUND: Experimental studies in rodents suggest that polybrominated diphenyl ethers (PBDEs) and poly- and perfluoroalkyl substances (PFAS) may contribute to depressive symptoms. Few studies have examined the impact of these chemicals on depression in adults.OBJECTIVE: To examine the associations between serum PBDE and PFAS concentrations during pregnancy and repeated measures of depressive symptoms in women assessed from pregnancy to 8 years postpartum.METHODS: This study was based on 377 women from the Health Outcomes and Measures of the Environment Study, a birth cohort in Cincinnati, OH (USA). PBDEs (BDE-28, -47, -99, -100, -153, and ∑PBDEs) and PFAS (perfluorooctanoate [PFOA], perfluorooctane sulfonate [PFOS], perfluorohexane sulfonate [PFHxS], perfluorononanoate [PFNA]) were quantified in maternal serum at 16 ± 3 weeks gestation. Depressive symptoms were measured using the Beck Depression Inventory-II (BDI-II) at ~20 weeks gestation and up to seven times during postpartum visits (4 weeks, 1, 2, 3, 4, 5, and 8 years). We used linear mixed models to estimate covariate-adjusted associations between chemical concentrations and repeated measures of BDI-II. Multinomial logistic regression models were used to estimate the relative risk ratios of having a medium or high depression trajectory.RESULTS: We found that a 10-fold increase in BDE-28 at 16 ± 3 weeks gestation was associated with significantly increased BDI-II scores (β = 2.5 points, 0.95 confidence interval [CI] 0.8, 4.2) from pregnancy to 8 years postpartum. Significant positive associations were also observed with BDE-47, -100, -153, and ∑PBDEs. A 10-fold increase in ∑PBDEs was associated with a 4.6-fold increased risk (95% CI 1.8, 11.8) of a high trajectory for BDI-II compared to a low trajectory. We observed no significant associations between PFAS and BDI-II scores.CONCLUSION: PBDEs during pregnancy were associated with more depressive symptoms among women in this cohort.	●	●							-		B	-
1031	ヒト（発達神経毒性）	Vuong, A. M.; Yolton, K.; Xie, C.; Dietrich, K. N.; Braun, J. M.; Webster, G. M.; Calafat, A. M.; Lanphear, B. P.; Chen, A.	Prenatal and childhood exposure to poly- and perfluoroalkyl substances (PFAS) and cognitive development in children at age 8 years	2019	Environ Res. 2019 May;172:242-248. doi: 10.1016/j.envres.2019.02.025. Epub 2019 Feb 16.	BACKGROUND: Toxicological studies indicate that poly- and perfluoroalkyl substances (PFAS) may be neurotoxic, but human studies have yet to provide compelling evidence for PFAS' impact on cognitive abilities.OBJECTIVE: To test whether prenatal and childhood PFAS are associated with cognitive abilities at 8 years and whether sex modifies these associations.METHODS: We included 221 mother-child pairs from the Health Outcomes and Measures of the Environment (HOME) Study, a birth cohort in Cincinnati, OH (USA). We quantified PFAS in maternal serum at 16 ± 3 weeks gestation and in child serum at 3 and 8 years. We used the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) at age 8 years, assessing Full Scale IQ (FSIQ), verbal comprehension, perceptual reasoning, working memory, and processing speed. We used multiple informant models to estimate covariate-adjusted differences in WISC-IV scores by repeated ln-transformed PFAS.RESULTS: Prenatal and childhood perfluorooctane sulfonate (PFOS) and perfluorohexane sulfonate (PFHxS) were not associated with WISC-IV measures. We observed an increase of 4.1-points (95% CI 0.3, 8.0) and 5.7-points (95% CI 1.2, 10.2) in working memory with 1-ln unit increase in prenatal perfluorooctanoate (PFOA) and perfluorononanoate (PFNA), respectively. In addition, PFNA at 3 years was associated with better FSIQ and perceptual reasoning. Child sex modified the relationship between prenatal PFOA and FSIQ; the association was positive in females only. Sex also modified the association between concurrent PFOS and FSIQ, with males having higher scores.CONCLUSION: We did not observe adverse associations between prenatal and childhood PFAS and cognitive function at age 8 years.	●	●							-	1	A	-
1032	ヒト（発達神経毒性）	Weng, J.; Hong, C.; Tasi, J.; Shen, C. Y.; Su, P.; Wang, S.	The association between prenatal endocrine-disrupting chemical exposure and altered resting-state brain fMRI in teenagers	2020	Brain Struct Funct. 2020 Jun;225(5):1669-1684. doi: 10.1007/s00429-020-02089-4. Epub 2020 May 25.	Many studies have reported that prenatal exposure to endocrine-disrupting chemicals (EDCs) can cause adverse behavioral effects or cognitive dysfunction in children. This study aimed to investigate a relationship of the concentration of prenatal EDCs and brain function in teenagers. We recruited 59 mother-child pairs during the third trimester of pregnancy, and collected and examined the concentration of EDCs, such as heavy metals, phthalates and perfluoroalkyl substances (PFASs), in maternal urine and serum. Resting-state functional magnetic resonance imaging (rs-fMRI) data were collected in teenagers 13-16 years of age, and fractional amplitude of low-frequency fluctuation (fALFF) and regional homogeneity (ReHo) were performed to find the association between maternal EDC concentrations and the functional development of the teenage brain. We found a correlation between MBP concentration and activity in the superior frontal gyrus, middle frontal gyrus, middle temporal gyrus and inferior temporal gyrus in the combined group of boys and girls. We also observed a correlation between MBzP concentration and activity in the anterior cingulum gyrus and insula in girls. We found a correlation between lead concentration and activity in the cuneus in the combined group. We also observed a correlation between MeHg concentration and activity in the superior temporal gyrus, caudate nucleus and putamen in the combined group. The PFOS results revealed a negative relationship between activity in the right putamen in boys, girls and the combined group after phthalate or heavy metals were applied as covariates. The PFNA results showed a negative correlation between activity in the left/right putamen and left caudate nucleus in boys, girls and the combined group after phthalate, heavy metals or PFOS were applied as covariates. We examined the correlations between maternal EDC concentrations and brain development and found that the associations with resting-state teenage brains in some circumstances are sex-related.	●	●							-	1	A	-
1033	ヒト（神経毒性）	Berg, Vivian; Nøst, Therese Haugdahl; Huber, Sandra; Rylander, Charlotta; Hansen, Solrunn; Veyhe, Anna Sofía; Fuskevåg, Ole Martin; Odland, Jon Øyvind; Sandanger, Torkjel Manning	Maternal serum concentrations of per- and polyfluoroalkyl substances and their predictors in years with reduced production and use	2014	Environ Int. 2014 Aug;69:58-66. doi: 10.1016/j.envint.2014.04.010. Epub 2014 May 7.	Determining maternal concentrations of per- and polyfluoroalkyl substances (PFASs) and the relative impact of various demographic and dietary predictors is important for assessing fetal exposure and for developing proper lifestyle advisories for pregnant women. This study was conducted to investigate maternal PFAS concentrations and their predictors in years when the production and use of several PFASs declined, and to assess the relative importance of significant predictors. Blood from 391 pregnant women participating in The Northern Norway Mother-and-Child Contaminant Cohort Study (MISA) was collected in the period 2007-2009 and serum analyses of 26 PFASs were conducted. Associations between PFAS concentrations, sampling date, and demographic and dietary variables were evaluated by multivariate analyses and linear models including relevant covariates. Parity was the strongest significant predictor for all the investigated PFASs, and nulliparous women had higher concentrations compared to multiparous women (10 ng/mL versus 4.5 ng/mL in median PFOS, respectively). Serum concentrations of PFOS and PFOA of women recruited day 1-100 were 25% and 26% higher, respectively, compared to those women recruited in the last 167 days of the study (day 601-867), and the concentrations of PFNA, PFDA and PFUnDA increased with age. Dietary predictors explained 0-17% of the variation in concentrations for the different PFASs. Significantly elevated concentrations of PFOS, PFNA, PFDA and PFUnDA were found among high consumers of marine food. The concentrations of PFHxS, PFHpS and PFNA were also increased in high consumers of game and elevated concentrations of PFHpS and PFOS were detected in high consumers of white meat. Study subjects with a high intake of salty snacks and beef had significantly higher concentrations of PFOA. The present study demonstrates that parity, sampling date and birth year are the most important predictors for maternal PFAS concentrations in years following a decrease in production and use of several PFASs. Further, dietary predictors of PFAS concentrations were identified and varied in importance according to compound.			●						-		B	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1034	ヒト（神経毒性）	Gump, Brooks B; Wu, Qian; Dumas, Amy K; Kannan, Kurunthachalam	Perfluorochemical (PFC) exposure in children: associations with impaired response inhibition	2011	Environ Sci Technol. 2011 Oct 1;45(19):8151-9. doi: 10.1021/es103712g. Epub 2011 Jun 17.	BACKGROUND: Perfluorinated chemicals (PFCs) have been used widely in consumer products since the 1950s and are currently found at detectable levels in the blood of humans and animals across the globe. In stark contrast to this widespread exposure to PFCs, there is relatively little research on potential adverse health effects of exposure to these chemicals. OBJECTIVES: We performed this cross-sectional study to determine if specific blood PFC levels are associated with impaired response inhibition in children. METHODS: Blood levels of 11 PFCs were measured in children (N = 83) and 6 PFCs: perfluorooctane sulfonate (PFOS), perfluorohexane sulfate (PFHxS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorooctanesulfonamide (PFOSA), and perfluorodecanoic acid (PFDA) - were found at detectable levels in most children (87.5% or greater had detectable levels). These levels were analyzed in relation to the differential reinforcement of low rates of responding (DRL) task. This task rewards delays between responses (i.e., longer inter-response times; IRTs) and therefore constitutes a measure of response inhibition. RESULTS: Higher levels of blood PFOS, PFNA, PFDA, PFHxS, and PFOSA were associated with significantly shorter IRTs during the DRL task. The magnitude of these associations was such that IRTs during the task decreased by 29-34% for every 1 SD increase in the corresponding blood PFC. CONCLUSIONS: This study suggests an association between PFC exposure and children's impulsivity. Although intriguing, there is a need for further investigation and replication with a larger sample of children.			●	●	●					-		B	-
1035	ヒト（神経毒性）	Power, Melinda C; Webster, Thomas F; Baccarelli, Andrea A; Weisskopf, Marc G	Cross-sectional association between polyfluoroalkyl chemicals and cognitive limitation in the National Health and Nutrition Examination Survey	2013	Neuroepidemiology. 2013;40(2):125-32. doi: 10.1159/000342310. Epub 2012 Oct 24.	BACKGROUND/AIMS: Our limited understanding of how polyfluoroalkyl chemicals (PFCs) may impact on human health suggests the potential for a protective impact on brain health. This study was designed to explore the association between PFCs and cognitive ability in older adults. METHODS: We assessed the association between four PFCs, perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorononanoic acid (PFNA) and perfluorohexane sulfonic acid (PFHxS), and self-reported limitation due to difficulty remembering or periods of confusion using data from participants aged 60-85 years from the 1999-2000 and 2003-2008 National Health and Nutrition Examination Surveys. We also considered whether diabetic status or diabetic medication use modifies this association in light of in vitro evidence that PFCs may act on the same receptors as some diabetic medications. RESULTS: In multivariable adjusted models, point estimates suggest a protective association between PFCs and self-reported cognitive limitation (odds ratio, OR; 95% confidence interval, CI) for a doubling in PFC concentration: PFOS (OR, 0.90; 95% CI, 0.78, 1.03), PFOA (OR, 0.92; 95% CI, 0.78, 1.09), PFNA (OR, 0.91; 95% CI, 0.79, 1.04) and PFHxS (OR, 0.93; 95% CI, 0.82, 1.06). The protective association was concentrated in diabetics, with strong, significant protective associations in nonmedicated diabetics. CONCLUSIONS: This cross-sectional study suggests that there may be a protective association between exposure to PFCs and cognition in older adults, particularly diabetics.				●	●						-		B	-
1036	ヒト（神経毒性）	Stein, Cheryl R; Savitz, David A	Serum perfluorinated compound concentration and attention deficit/hyperactivity disorder in children 5-18 years of age	2011	Environ Health Perspect. 2011 Oct;119(10):1466-71. doi: 10.1289/ehp.1003538. Epub 2011 Jun 10.	BACKGROUND: Perfluorinated compounds (PFCs) are persistent environmental pollutants. Toxicology studies demonstrate the potential for perfluorooctanoic acid (PFOA) and other PFCs to affect human growth and development. Attention deficit/hyperactivity disorder (ADHD) is a developmental disorder with suspected environmental and genetic etiology. OBJECTIVES: We examined the cross-sectional association between serum PFC concentration and parent or self-report of doctor-diagnosed ADHD with and without current ADHD medication. METHODS: We used data from the C8 Health Project, a 2005-2006 survey in a Mid-Ohio Valley community highly exposed to PFOA through contaminated drinking water, to study non-Hispanic white children 5-18 years of age. Logistic regression models were adjusted for age and sex. RESULTS: Of the 10,546 eligible children, 12.4% reported ADHD and 5.1% reported ADHD plus ADHD medication use. We observed an inverted J-shaped association between PFOA and ADHD, with a small increase in prevalence for the second quartile of exposure compared with the lowest, and a decrease for the highest versus lowest quartile. The prevalence of ADHD plus medication increased with perfluorohexane sulfonate (PFHxS) levels, with an adjusted odds ratio of 1.59 (95% confidence interval, 1.21-2.08) comparing the highest quartile of exposure to the lowest. We observed a modest association between perfluorooctane sulfonate and ADHD with medication. CONCLUSIONS: The most notable finding for PFOA and ADHD, a reduction in prevalence at the highest exposure level, is unlikely to be causal, perhaps reflecting a spurious finding related to the geographic determination of PFOA exposure in this population or to unmeasured behavioral or physiologic correlates of exposure and outcome. Possible positive associations between other PFCs and ADHD, particularly PFHxS, warrant continued investigation.				●	●	●	●				-		B	-
1037	ヒト（腎毒性）	Arrebola, J. P.; Ramos, J. J.; Bartolomé, M.; Esteban, M.; Huetos, O.; Cañas, A. I.; López-Herranz, A.; Calvo, E.; Pérez-Gómez, B.; Castaño, A.; BIOAMBIENT.ES,	Associations of multiple exposures to persistent toxic substances with the risk of hyperuricemia and subclinical uric acid levels in BIOAMBIENT	2019	Environ Int 123: 512-521. doi: 10.1016/j.envint.2018.12.030. Epub 2019 Jan 5.	Hyperuricemia is becoming a serious public health issue, which is highly influenced by environmental factors, although there is still controversial information on the potential influence of the exposure to Persistent Toxic Substances (PTSs) in the general population. In this study we aimed to assess the association. PTS exposure with uric acid homeostasis in a sample of the Spanish population. Participants were recruited during 2009-2010 in all the main geographical areas of Spain. Exposure to 34 PTSs was estimated by chemical analyses of serum levels of 6 Polychlorinated Biphenyls (PCBs, n = 950), 13 Organochlorine Pesticides (OCPs, n = 453), 6 Perfluoroalkyl Substances (PFAs, n = 755), 7 Polybrominated Diphenyl Ethers (PBDEs, n = 365), urinary Cadmium (n = 926), and Lead in whole blood (n = 882). The two study outcomes were defined as the prevalence of hyperuricemia in the study population and uric acid levels, the latter only in individuals with no previous diagnosis of hyperuricemia. Statistical analyses were performed by means of binomial logistic regression and linear regression, and mixture effects were screened using Weighted Quantile Sum Regression (WQS). Serum concentrations of γ-HCH, o,p´-DDE, PCB-138, PCB-153, PFOA, and urinary Cadmium were associated with an increased risk of hyperuricemia, while PBDE-153 showed an inverse association with the effect. Furthermore, exposure to Cadmium, PCB-138, and to PCB-153 was positively associated with uric acid levels. Results were consistent after lipid adjustment or standardization. WQS analyses revealed a major contribution of PCB-153 within the PCB mixture on both the risk of hyperuricemia and uric acid levels. Sensitivity analyses were performed by adjusting for dietary habits, fasting glucose and estimated glomerular filtration rate. Overall, we found novel associations between human exposure to mixtures of PTSs and disturbances in uric acid homeostasis. However, we cannot completely rule out potential residual confounding effect or reversed-causality related to the cross-sectional design.			●	●							-		C	B
1038	ヒト（腎毒性）	Conway, B. N.; Badders, A. N.; Costacou, T.; Arthur, J. M.; Innes, K. E.	Perfluoroalkyl substances and kidney function in chronic kidney disease, anemia, and diabetes	2018	Diabetes Metab Syndr Obes. 2018 Nov 15;11:707-716. doi: 10.2147/DMSO.S173809. eCollection 2018.	Background: Anemia often complicates chronic kidney disease (CKD), leading to insufficient tissue oxygenation and hypoxic injury, the factor thought to underlie progression from CKD to renal failure. Perfluorocarbons are potent oxygen transporters used in organ preservation and synthetic blood development. Data are scarce on their relationship with kidney function, especially in diabetes where anemia and hypoxia are more prevalent. We investigated the relationship of perfluoroalkyl acids (PFAS) with kidney function and variation by diabetes and anemia status.Methods: Data on 53650 adults (5,210 with diabetes) were obtained from the C8 Health Project. CKD was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m2. Four PFAS were investigated: perfluorohexane sulfonate (PFHxS), perfluorooctanoic acid, perfluorooctane sulfonate, and perfluorononanoic acid.Findings: Each PFAS was positively associated with eGFR among those with CKD or anemia; this was the strongest among those with both CKD and anemia, followed by those with CKD uncomplicated by anemia. These relationships were more pronounced among those with diabetes (all P<0.01). In the absence of both CKD and anemia, PFAS was inversely associated with eGFR. Among persons with both anemia and diabetes, when further stratified by CKD stage, compared to an eGFR <30, ORs (95% CI) for being in the eGFR ≥ 90, 60-89, 45-59, and 30-45 range, respectively, were 3.2 (2.00-5.13), 2.64 (1.83-3.80), 3.18 (2.17-4.67), and 1.99 (1.38-2.86) for each ng/dL increase in PFHxS. Results were similar for each PFAS.Interpretation: PFAS are inversely associated with kidney function in CKD and diabetes, with a stronger relation observed when anemia is present.			●	●							-	1	A	B
1039	ヒト（腎毒性）	Dhingra, R.; Lally, C.; Darrow, L. A.; Klein, M.; Winquist, A.; Steenland, K.	Perfluorooctanoic acid and chronic kidney disease: Longitudinal analysis of a Mid-Ohio Valley community	2016	Environ Res 145: 85-92. doi: 10.1016/j.envres.2015.11.018. Epub 2015 Dec 6.	INTRODUCTION: Perfluorooctanoic acid (PFOA) is an environmentally persistent chemical found at low-levels in the serum of almost all U.S. residents. Chronic kidney disease (CKD) has been positively associated with serum PFOA in prior cross-sectional studies and in one occupational mortality study, while other investigations have found no association between kidney function and PFOA.METHODS: We conducted a longitudinal analysis of chronic kidney disease among adults, aged ≥20 years, (N=32,254) in a Mid-Ohio Valley community cohort, exposed to high PFOA levels from contaminated drinking water. Estimated retrospective yearly serum PFOA concentrations (1951-2011) were previously modeled in this population. Information about lifetime history of CKD diagnosis was collected during surveys in 2008-2011; self-reported CKD diagnoses were validated through medical record review. Using a Cox proportional hazards model, we retrospectively examined the association between validated adult onset CKD, and modeled PFOA exposure, from time of first exposure. We also analyzed data for the cohort prospectively, among people with no CKD diagnosis prior to enrollment in a baseline survey in 2005-2006. Both the full cohort and a non-diabetic subset were analyzed, retrospectively and prospectively.RESULTS: Neither in retrospective nor in prospective analyses did we find a significant (α=0.05) trend between PFOA exposure and CKD. In the full cohort, estimated hazard ratios by quintile of cumulative serum PFOA in the retrospective analysis were 1 (referent), 1.26, 1.12, 1.12 and 1.24 (trend test for log cumulative exposure: p=0.80).CONCLUSION: Our analyses suggest that CKD is not associated with exposure to PFOA.			●	●		●					-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ラン①	文献ラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1040	ヒト（腎毒性）	Jain, R. B.; Ducatman, A.	Dynamics of associations between perfluoroalkyl substances and uric acid across the various stages of glomerular function	2019	Environ Res. 2019 Apr;26(12):12425-12434. doi: 10.1007/s11356-019-04666-5. Epub 2019 Mar 7.	Associations between selected perfluoroalkyl acids (PFAAs) and biomarkers of renal function were evaluated for US adult aged ≥ 20 years (N = 8220) in the National Health and Nutrition Examination Survey for 2005-2014. Glomerular filtration (GF) stage-stratified regression models were classified by estimated glomerular filtration rate (eGFR) with GF-1 (eGFR > 90 mL/min/1.73 m2), GF-2 (eGFR 60-89 mL/min/1.73 m2), GF-3A (45-59 mL/min/1.73 m2), and GF-3B/4 (15-44 mL/min/1.73 m2). For GF-1, PFOA, PFOS, and PFHxS were positively and significantly associated with serum creatinine. Serum albumin levels were positively associated with the PFAA considered at all stages and most associations were significant. Further, PFAS serum concentration associations to serum albumin were about 44595 times stronger at GF-3B/4 than at GF-1. In contrast, urine albumin was negatively and significantly associated with PFOA and PFHxS serum concentrations at all stages of renal function, while, PFOS and PFNA were negatively and significantly associated to urine albumin at GF-3A and GF-3B/4. Urine albumin/creatinine ratios were negatively and significantly associated with PFOA, PFOS, and, and PFHxS serum concentrations at all stages of renal function, as well as with PFNA and PFDA at GF-3A and GF-3B/4. Recent work revealed that serum PFAAs have an inverted U-shaped association to the calculated stages of renal failure based on eGFR; this work adds that albuminuria makes additional negative contributions to already existing negative associations of PFAA to eGFR in advancing stages of renal failure. We hypothesize that both progressive renal failure per se and especially renal failure with albuminuria cause the kidneys to reabsorb less and to excrete more of the PFAAs studied. We suspect this finding may generalize to some other perfluoroalkyl substances (PFAS). The findings also imply study design considerations for evaluating associations to diseases and biomarkers associated with renal failure, such as diabetes.	●	●							-		B	B
1041	ヒト（腎毒性）	Jain, R. B.; Ducatman, A.	Perfluoroalkyl acids serum concentrations and their relationship to biomarkers of renal failure: Serum and urine albumin, creatinine, and albumin creatinine ratios across the spectrum of glomerular function among US adults	2019	Environ Res. 2019 Jul;174:143-151. doi: 10.1016/j.envres.2019.04.034. Epub 2019 May 4.	National Health and Nutrition Examination Survey 2007-2014 data (N = 6844) for adults aged ≥ 20 years were analyzed to estimate associations of perfluoroalkyl substances (PFAS), namely, PFOA, PFOS, PFDA, PFHxS, and PFNA with uric acid across stages of declining glomerular function. The population was stratified by the estimated glomerular filtration rates (eGFR) stages accompanying kidney disease: GF-1 with eGFR > 90 mL/min/1.73 m2; GF-2 with eGFR 60-89 mL/min/1.73 m2; GF-3A with eGFR 45-59 mL/min/1.73 m2; and GF-3B/4 with eGFR 15-44 mL/min/1.73 m2. Adjusted and unadjusted geometric means of uric acid increased from GF-1 to GF-3B/4 for males and females. Adjusted geometric means for uric acid were higher for males by 1.38, 1.03, and 0.62 mg/dL for GF-1, GF2, and GF-3 respectively but for GF-3B/4, females had higher adjusted geometric means than males by 0.16 mg/dL, revealing narrowing of sex differences in uric acid as glomerular function declines. The direction of association between PFAS and uric acid was positive for GF-1 and GF-2 for males and for every PFAS except PFDA for females. For males for GF-3B/4, association between every PFAS except PFHxS and uric acid was found to be negative (p < 0.01). For females, only PFHxS actually reverses its relationship with increasing stages of renal disease. Uric acid associations with PFAS reverse in males with advanced renal failure. An implication is that previously reported association of PFAS exposure with uric acid is not due to renal failure. Understanding of other biomarkers associated with both PFAS exposure and renal failure may benefit from similar evaluation.	●	●							-		B	B
1042	ヒト（腎毒性）	Kataria, A.; Trachtman, H.; Malaga-Dieguez, L.; Trasande, L.	Association between perfluoroalkyl acids and kidney function in a cross-sectional study of adolescents	2015	Environ Health 14: 89. doi: 10.1186/s12940-015-0077-9.	BACKGROUND: Perfluoroalkyl acids are synthetic compounds widely used in industrial and commercial applications. Laboratory studies suggest that these persistent and bioaccumulative chemicals produce oxidant stress and damage glomerular endothelial cells, raising concern regarding the impact of these compounds on renal function.METHODS: We performed cross-sectional analyses of data 1960 participants aged 44914 years of the 2003-2010 National Health and Nutrition Examination Surveys. PFAA exposure was assessed using levels of perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid, and perfluorohexane sulfonic acid. Primary study outcomes were estimated glomerular filtration rate (eGFR) and serum uric acid.RESULTS: While adjusting for demographics, cotinine, prehypertension, insulin resistance, body mass index, and hypercholesterolemia, adolescents in the highest PFOA and PFOS quartile had a lower eGFR, 6.84 mL/min/1.73 m(2) (95% CI: 2.19 to 11.48) and 9.69 mL/min/1.73 m(2) (95 % CI: -4.59 to 14.78), respectively, compared to the lowest quartile. Highest PFOA and PFOS quartiles were also associated with 0.21 mg/dL (95% CI: 0.056 to 0.37) and 0.19 mg/dL (95% CI: 0.032 to 0.34) increases in uric acid, respectively.CONCLUSIONS: PFAAs are associated with a reduction in kidney function and increased uric acid levels in otherwise healthy adolescents. Reverse causation and residual confounding could explain the results. Our study results confirm and amplify previous findings, though longitudinal studies examining prenatal and childhood biomarkers in relationship with robust measures of childhood renal function are needed.	●	●	●	●					-		B	B
1043	ヒト（腎毒性）	Lee, Jeonghwan; Oh, Sohee; Kang, Habyeong; Kim, Sunmi; Lee, Gowoon; Li, Lilin; Kim, Clara Tammy; An, Jung Nam; Oh, Yun Kyu; Lim, Chun Soo; Kim, Dong Ki; Kim, Yon Su; Choi, Kyungho; Lee, Jung Pyo	Environment-wide association study of CKD	2020	Clin J Am Soc Nephrol. 2020 Jun 8;15(6):766-775. doi: 10.2215/CJN.06780619. Epub 2020 May 22.	BACKGROUND AND OBJECTIVES: Exposure to environmental chemicals has been recognized as one of the possible contributors to CKD. We aimed to identify environmental chemicals that are associated with CKD. DESIGN, SETTING, PARTICIPANTS, & MEASUREMENTS: We analyzed the data obtained from a total of 46,748 adults who participated in the National Health and Nutrition Examination Survey (1999-2016). Associations of chemicals measured in urine or blood (n=262) with albuminuria (urine albumin-to-creatinine ratio ≥30 mg/g), reduced eGFR (<60 ml/min per 1.73 m(2)), and a composite of albuminuria or reduced eGFR were tested and validated using the environment-wide association study approach. RESULTS: Among 262 environmental chemicals, seven (3%) chemicals showed significant associations with increased risk of albuminuria, reduced eGFR, or the composite outcome. These chemicals included metals and other chemicals that have not previously been associated with CKD. Serum and urine cotinines, blood 2,5-dimethylfuran (a volatile organic compound), and blood cadmium were associated with albuminuria. Blood lead and cadmium were associated with reduced eGFR. Blood cadmium and lead and three volatile compounds (blood 2,5-dimethylfuran, blood furan, and urinary phenylglyoxylic acid) were associated with the composite outcome. A total of 23 chemicals, including serum perfluorooctanoic acid, seven urinary metals, three urinary arsenics, urinary nitrate and thiocyanate, three urinary polycyclic aromatic hydrocarbons, and seven volatile organic compounds, were associated with lower risks of one or more manifestations of CKD. CONCLUSIONS: A number of chemicals were identified as potential risk factors for CKD among the general population.	●	●							-		C	C
1044	ヒト（腎毒性）	Lin, C. Y.; Lin, L. Y.; Wen, T. W.; Lien, G. W.; Chien, K. L.; Hsu, S. H.; Liao, C. C.; Sung, F. C.; Chen, P. C.; Su, T. C.	Association between levels of serum perfluorooctane sulfate and carotid artery intima-media thickness in adolescents and young adults	2013	Int J Cardiol. 2013 Oct 9;168(4):3309-16. doi: 10.1016/j.ijcard.2013.04.042. Epub 2013 May 7.	BACKGROUND: Perfluorinated chemicals (PFCs) have been widely used for years in a variety of products worldwide. Although epidemiological findings have shown that PFC levels are positively associated with cholesterol and uric acid levels, it is unknown whether PFCs are associated with atherosclerosis.METHODS: We recruited 664 subjects (12-30 years) from a population-based sample of adolescents and young adults based on a mass urine screening to determine the relationship between serum levels of PFCs and carotid intima-media thickness (CIMT).RESULTS: The median concentrations and ranges of perfluorooctanoic acid (PFOA), perfluorooctane sulfate (PFOS), perfluorononanoic acid (PFNA), and perfluorodecanoic acid (PFUA) were 3.49 (0.75-52.2) ng/mL, 8.65 (0.11-85.90) ng/mL, 0.38 (0.38-25.4) ng/mL, and 6.59 (1.50-105.7) ng/mL, respectively. After controlling for age, gender, smoking status, systolic blood pressure, body mass index, low-density lipoprotein cholesterol, triglyceride, high-sensitivity C-reactive protein, and homeostasis model assessment of insulin resistance, multiple linear regression analysis revealed that CIMT increased significantly across quartiles of PFOS (0.434 mm, 0.446 mm, 0.458 mm, 0.451 mm; P for trend <0.001). Subpopulation analysis showed the association between PFOS and CIMT was more evident and significant in females, non-smokers, subjects of age 44914 years, BMI<24, and those with APOE genotype of E2 carrier and E3/E3. CONCLUSIONS: Higher serum concentrations of PFOS were associated with an increase of carotid IMT in this cohort of adolescents and young adults. Further studies are warranted to clarify the causal relationship between PFOS and atherosclerosis.	●	●	●	●			●		-		B	B
1045	ヒト（腎毒性）	Nielsen, C.; Andersson Hall, U.; Lindh, C.; Ekström, U.; Xu, Y.; Li, Y.; Holmäng, A.; Jakobsson, K.	Pregnancy-induced changes in serum concentrations of perfluoroalkyl substances and the influence of kidney function	2020	Environ Health. 2020 Jul 8;19(1):80. doi: 10.1186/s12940-020-00626-6.	Epidemiological associations between maternal concentrations of perfluoroalkyl substances (PFAS) and birth weight are inconsistent. There is concern that studies based on samples collected in late pregnancy may be confounded by kidney function but studies of the relation between pregnancy-induced changes in PFAS and kidney function are lacking. Our aims were to investigate changes in serum concentrations of perfluorononanoic acid (PFNA), perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS) and perfluorohexane sulfonate (PFHxS) from early to late pregnancy and to explore relations to changes in glomerular filtration rate (GFR) and glomerular pore size.	●	●							-		D	B
1046	ヒト（腎毒性）	Qin, X. D.; Qian, Z.; Vaughn, M. G.; Huang, J.; Ward, P.; Zeng, X. W.; Zhou, Y.; Zhu, Y.; Yuan, P.; Li, M.; Bai, Z.; Paul, G.; Hao, Y. T.; Chen, W.; Chen, P. C.; Dong, G. H.; Lee, Y. L.	Positive associations of serum perfluoroalkyl substances with uric acid and hyperuricemia in children from Taiwan	2016	Environ Pollut. 2016 May;212:519-524. doi: 10.1016/j.envpol.2016.02.050. Epub 2016 Mar 10.	To investigate the risk of hyperuricemia in relation to Perfluoroalkyl substances (PFASs) in children from Taiwan, 225 Taiwanese children aged 12-15 years were recruited from 2009 to 2010 Linear and logistic regression models were employed to examine the influence of PFASs on serum uric acid levels. Findings revealed that eight of ten PFASs analyses were detected in >94% of the participants' serum samples. Multivariate linear regression models revealed that perfluorooctanic acid (PFOA) was positively associated with serum uric acid levels (β = 0.1463, p < 0.05). Of all the PFASs analyses, only PFOA showed a significant effect on elevated levels of hyperuricemia (aOR = 2.16, 95%CI: 1.29-3.61). When stratified by gender, the association between serum PFOA and uric acid levels was only evident among boys (aOR = 2.76, 95%CI: 1.37-5.56). In conclusion, PFOA was found to be associated with elevated serum levels of uric acid in Taiwanese children, especially boys. Further research is needed to elucidate these links.	●	●	●	●					-		B	B
1047	ヒト（腎毒性）	Scinicariello, F.; Buser, M. C.; Balluz, L.; Gehle, K.; Murray, H. E.; Abadin, H. G.; Attanasio, R.	Perfluoroalkyl acids, hyperuricemia and gout in adults: Analyses of NHANES 2009-2014	2020	Chemosphere. 2020 Nov;259:127446. doi: 10.1016/j.chemosphere.2020.127446. Epub 2020 Jun 20.	Background: Previous studies have reported a positive association of perfluoralkyl acids (PFAAs), including perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), with hyperuricemia. The objective of the study is to investigate whether there is an association between concurrent serum levels of several PFAAs and gout, serum uric acid (SUA) or hyperuricemia in the U.S. adult population as represented by the National Health and Nutrition Examination Survey (NHANES) 2009e2014 sample (n ¼ 4917). The PFAAs investigated include PFOA, perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluorohexane sulfonic acid (PFHxS) and PFOS.	●	●							-		D	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ラン①C	文献ラン②B
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1048	ヒト（腎毒性）	Shankar, A.; Xiao, J.; Ducatman, A.	Perfluoroalkyl chemicals and chronic kidney disease in US adults	2011	Am J Epidemiol. 2011 Oct 15;174(8):893-900. doi: 10.1093/aje/kwr171. Epub 2011 Aug 26.	Chronic kidney disease (CKD) is a major public health problem. Identifying novel risk factors for CKD, including widely prevalent environmental exposures, is therefore important. Perfluoroalkyl chemicals (PFCs), including perfluorooctanoic acid and perfluorooctane sulfonate, are manmade chemicals that have been detected in the blood of more than 0.98 of the US population. Results from experimental animal studies have suggested that an association between PFCs and CKD is plausible. However, in humans, the relation between serum PFCs and CKD has not been examined. The authors examined the relation of serum PFCs and CKD in 4587 adult participants (51.1% women) from the combined 1999-2000 and 2003-2008 cycles of the National Health and Nutritional Examination Survey for whom PFC measurements were available. The main outcome was CKD, defined as a glomerular filtration rate of less than 60 mL/minute/1.73 m(2). The authors found that serum levels of PFCs, including perfluorooctanoic acid and perfluorooctane sulfonate, were positively associated with CKD. This association was independent of confounders such as age, sex, race/ethnicity, body mass index, diabetes, hypertension, and serum cholesterol level. Compared with subjects in quartile 1 (referent), the multivariable odds ratio for CKD among subjects in quartile 4 was 1.73 (95% confidence interval: 1.04, 2.88; P for trend = 0.015) for perfluorooctanoic acid and 1.82 (95% confidence interval: 1.01, 3.27; P for trend = 0.019) for perfluorooctane sulfonate. The present results suggest that elevated PFC levels are associated with CKD.	●	●		●	●					-		C	B
1049	ヒト（腎毒性）	Steenland, K.; Tinker, S.; Shankar, A.; Ducatman, A.	Association of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) with uric acid among adults with elevated community exposure to PFOA	2010	Environ Health Perspect. 2010 Feb;118(2):229-33. doi: 10.1289/ehp.0900940.	BACKGROUND: Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) are compounds that do not occur in nature, have been widely used since World War II, and persist indefinitely in most environments. Median serum levels in the United States are 4 ng/mL for PFOA and 21 ng/mL for PFOS. PFOA has been associated with elevated uric acid in two studies of chemical workers. Uric acid is a risk factor for hypertension and possibly other cardiovascular outcomes.METHODS: We conducted a cross-sectional study of PFOA and PFOS and uric acid among 54951 adult community residents in Ohio and West Virginia, who lived or worked in six water districts contaminated with PFOA from a chemical plant. Analyses were conducted by linear and logistic regression, adjusted for confounders.RESULTS: Both PFOA and PFOS were significantly associated with uric acid. An increase of 0.20.3 mg/dL uric acid was associated with an increase from the lowest to highest decile of either PFOA or PFOS. Hyperuricemia risk increased modestly with increasing PFOA; the odds ratios by quintile of PFOA were 1.00, 1.33 [95% confidence interval (CI), 1.241.43], 1.35 (95% CI, 1.261.45), 1.47 (95% CI, 1.371.58), and 1.47 (95% CI, 1.371.58; test for trend, p < 0.0001). We saw a less steep trend for PFOS. Inclusion of both correlated fluorocarbons in the model indicated PFOA was a more important predictor than was PFOS.CONCLUSION: Higher serum levels of PFOA were associated with a higher prevalence of hyperuricemia, but the limitations of cross-sectional data and the possibility of noncausal mechanisms prohibit conclusions regarding causality.	●	●		●	●	●				-		B	B
1050	ヒト（腎毒性）	Wang, J.; Zeng, X. W.; Bloom, M. S.; Qian, Z.; Hinyard, L. J.; Belue, R.; Lin, S.; Wang, S. Q.; Tian, Y. P.; Yang, M.; Chu, C.; Gurram, N.; Hu, L. W.; Liu, K. K.; Yang, B. Y.; Feng, D.; Liu, R. Q.; Dong, G. H.	Renal function and isomers of perfluorooctanoate (PFOA) and perfluorooctanesulfonate (PFOS): Isomers of C8 Health Project in China	2019	Chemosphere. 2019 Mar;218:1042-1049. doi: 10.1016/j.chemosphere.2018.11.191. Epub 2018 Nov 28.	Perfluoroalkyl substances (PFASs) are widely-utilized synthetic chemicals commonly found in industrial and consumer products. Previous studies have examined associations between PFASs and renal function, yet the results are mixed. Moreover, evidence on the associations of isomers of PFASs with renal function in population from high polluted areas is scant. To help to address this data gap, we used high performance liquid chromatography-mass spectrometry to measure serum isomers of perfluorooctanoate (PFOA), perfluorooctanesulfonate (PFOS), and other PFASs from 1612 adults residing in Shenyang, China, and characterized their associations with estimated glomerular filtration rate (eGFR) and chronic kidney disease (CKD). Results showed that after adjusted for multiple confounding factors, most of the higher fluorinated PFASs, except for PFOA and PFDA, were negatively associated with eGFR and positively associated with CKD. Compared with linear PFOS (n-PFOS), branched PFOS isomers (Br-PFOS) were more strongly associated with eGFR (Br-PFOS; β = -1.22, 95%CI: 2.02, -0.42; p = 0.003 vs. n-PFOS; β = -0.16, 95%CI: 0.98, 0.65; p = 0.691) and CKD (Br-PFOS; OR = 1.27; 0.95 CI: 1.02, 1.58; p = 0.037 vs. n-PFOS; OR = 0.98; 0.95 CI: 0.80, 1.20; p = 0.834). In conclusion, branched PFOS isomers were negatively associated with renal function whereas their linear counterparts were not. Given widespread exposure to PFASs, potential nephrotoxic effects are of great public health concern, Furthermore, longitudinal research on the potential nephrotoxic effects of PFASs isomers will be necessary to more definitively assess the risk.	●									-	1	B	A
1051	ヒト（腎毒性）	Watkins, D. J.; Josson, J.; Elston, B.; Bartell, S. M.; Shin, H. M.; Vieira, V. M.; Savitz, D. A.; Fletcher, T.; Wellenius, G. A.	Exposure to perfluoroalkyl acids and markers of kidney function among children and adolescents living near a chemical plant	2013	Environ Health Perspect 121: 625-630. doi: 10.1289/ehp.1205838. Epub 2013 Mar 11.	BACKGROUND: Serum levels of perfluorooctanoic acid (PFOA) have been associated with decreased renal function in cross-sectional analyses, but the direction of the association is unclear.OBJECTIVES: We examined the association of measured and model-predicted serum PFOA concentrations with estimated glomerular filtration rate (eGFR), a marker of kidney function, in a highly exposed population (median serum PFOA, 28.3 ng/mL).METHODS: We measured serum creatinine, PFOA, perfluorooctane sulfonate (PFOS), perfluorononanoic acid (PFNA), and perfluorohexane sulfonate (PFHxS) and calculated eGFR in 9660 children 1 to < 18 years of age at study enrollment. We predicted concurrent and historical serum PFOA concentrations using a validated environmental, exposure, and pharmacokinetic model based on individual residential histories, and used linear regression to estimate the association between eGFR and measured and predicted serum PFOA concentrations. We hypothesized that predicted serum PFOA levels would be less susceptible to reverse causation than measured levels.RESULTS: An interquartile range increase in measured serum PFOA concentrations [IQR ln(PFOA) = 1.63] was associated with a decrease in eGFR of 0.75 mL/min/1.73 m(2) (95% CI: -1.41, -0.10; p = 0.02). Measured serum levels of PFOS, PFNA, and PFHxS were also cross-sectionally associated with decreased eGFR. In contrast, predicted serum PFOA concentrations at the time of enrollment were not associated with eGFR (-0.10; 0.95 CI: -0.80, 0.60; p = 0.78). Additionally, predicted serum PFOA levels at birth and during the first ten years of life were not related to eGFR.CONCLUSIONS: Our findings suggest that the cross-sectional association between eGFR and serum PFOA observed in this and prior studies may be a consequence of, rather than a cause of, decreased kidney function.	●	●	●	●						-		B	B
1052	ヒト（腎毒性）	Zeng, X. W.; Lodge, C. J.; Dharmage, S. C.; Bloom, M. S.; Yu, Y.; Yang, M.; Chu, C.; Li, Q. Q.; Hu, L. W.; Liu, K. K.; Yang, B. Y.; Dong, G. H.	Isomers of per- and polyfluoroalkyl substances and uric acid in adults: Isomers of C8 Health Project in China	2019	Environ Int. 2019 Dec;133(Pt A):105160. doi: 10.1016/j.envint.2019.105160. Epub 2019 Sep 10.	BACKGROUND: Greater levels of serum per- and polyfluoroalkyl substances (PFAS) are known to be associated with higher uric acid which itself leads to a number of chronic diseases. However, whether this association varies across PFAS isomers which recently have been found to be associated with human health remains unknown.OBJECTIVES: To address this research gap, we explored isomer-specific associations between serum PFAS and uric acid in Chinese adults.METHODS: We conducted a cross-sectional study of associations between serum PFAS isomer and serum uric acid in 1612 participants from the Isomer of C8 Health Project. We used multivariable linear and logistic regression models to analyze serum isomers of perfluorooctanoate (PFOA), perfluorooctane sulfonate (PFOS), and other PFASs as continuous and categorical predictors of uric acid, adjusted for confounders. The association was also stratified by kidney function stage based on estimated glomerular filtration rate (GF-1, GF-2, GF-3a, and GF-3b/4).RESULTS: We found positive associations between serum PFAS isomer concentrations and uric acid. Uric acid levels were greater for each log-unit increase in branched PFOA (β = 0.30, 0.95 CI: 0.21, 0.40), linear PFOA (β = 0.18, 0.95 CI: 0.09, 0.26), branched PFOS (β = 0.09, 0.95 CI: 0.02, 0.17) and linear PFOS (β = 0.06, 0.95 CI: -0.01, 0.14) concentration. The associations between PFAS and uric acid showed an inverted U' shaped pattern across kidney function stages. For example, uric acid level was greater with each log-unit increase in total-PFOA among GF-1 (β = 0.21, 0.95 CI: 0.06, 0.37), this relationship was greater in GF-3a (β = 0.49, 0.95 CI: 0.09, 0.89) and decreased in GF-3b/4 (β = -0.22, 0.95 CI: -0.83, 0.39). We also found the odds of hyperuricemia increased linearly with increasing branched PFOA in quartiles (odds ratio = 2.67, 0.95 CI: 1.86, 3.85 at the highest quartile).CONCLUSION: We report novel results in which PFAS associations with uric acid varied according to isomer and adult kidney function. Besides, our findings are consistent with previous epidemiologic studies in finding a positive association between serum PFAS concentrations and serum uric acid, especially for PFOA. Our results indicate that more research is needed to more clearly assess the impact of PFAS isomers on human health, which will help to refine regulation policies for PFAS.	●	●								-	1	B	A
1053	ヒト（肝毒性）	Gleason, Jessie A; Post, Gloria B; Fagliano, Jerald A	Associations of perfluorinated chemical serum concentrations and biomarkers of liver function and uric acid in the US population (NHANES), 2007-2010	2015	Environ Res. 2015 Jan;136:8-14. doi: 10.1016/j.envres.2014.10.004. Epub 2014 Nov 19.	BACKGROUND: Perfluorinated chemicals (PFCs) are a group of manmade compounds that are not broken down in the body. Four PFCs (PFHxS, PFOS, PFOA, and PFNA) have been found in the blood of more than 98% of the United States population. OBJECTIVES: Our goal was to assess associations between PFHxS, PFOS, PFOA, and PFNA and uric acid, alanine transferase (ALT), gamma-glutamyl transferase (GGT), asparate aminotransferase (AST), alkaline phosphate (ALP), and total bilirubin in 2007-2008 and 2009-2010 combined National Health and Nutrition Examination Survey (NHANES). METHODS: We used multivariate linear regression and logistic regression adjusted for age, gender, race/ethnicity and BMI group, poverty, smoking, and/or alcohol consumption to estimate associations. Trend analysis was performed. RESULTS: PFHxS was associated with ALT. Each quartile of PFOS was statistically associated with total bilirubin [(Q2: OR=1.44, 95% CI 1.12-1.84), (Q3: OR=1.65, 95% CI 1.25-2.18), and (Q4: OR=1.51, 95% CI 1.06-2.15)], with evidence of an increasing trend (p-value=0.028). PFOA was associated with uric acid, ALT, GGT, and total bilirubin. PFNA was linearly associated with ALT (p-value <0.001), and there was statistically significant increasing trend (p-value=0.042). CONCLUSIONS: Our analysis found evidence of associations of biomarkers of liver function and uric acid with PFHxS, PFOS, PFOA, and PFNA at levels found in the general U.S. population.			●	●		●				-	1	B	A

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ランク①	文献ランク②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1054	ヒト（腎毒性）	Shankar, Anoop; Xiao, Jie; Ducatman, Alan	Perfluoroalkyl chemicals and elevated serum uric acid in US adults	2011	Clin Epidemiol. 2011;3:251-8. doi: 10.2147/CLEP.S21677. Epub 2011 Sep 30.	BACKGROUND: Perfluoroalkyl chemicals, including perfluorooctanoic acid and perfluorooctane sulfonate, are man-made chemicals that have been detected in the blood of over 98% of the US population. Serum uric acid is a novel biomarker, even mild elevations of which has been implicated in the development of hypertension, diabetes mellitus, cardiovascular disease, and chronic kidney disease. We examined the relationship of serum perfluoroalkyl chemicals, including perfluorooctanoic acid and perfluorooctane sulfonate, and elevated uric acid levels in a representative sample of US adults. METHODS: We examined 3883 participants from the 1999-2000 and 2003-2006 National Health and Nutritional Examination Surveys, a representative, multiethnic population-based survey of noninstitutionalized US adults. Serum perfluorooctanoic acid and perfluorooctane sulfonate were analyzed as quartiles. The main outcome was hyperuricemia. RESULTS: We found that serum levels of perfluoroalkyl chemicals, including perfluorooctanoic acid and perfluorooctane sulfonate, were positively associated with hyperuricemia. This association appeared to be independent of confounders such as age, gender, race-ethnicity, body mass index, diabetes, hypertension, and serum cholesterol. Compared with subjects in quartile 1 (referent), the multivariate odds ratio for hyperuricemia among subjects in quartile 4 was 1.97 (95% confidence interval 1.44-2.70, P < 0.0001) for perfluorooctanoic acid and 1.48% (95% confidence interval 0.99-2.22, P = 0.0433) for perfluorooctane sulfonate. This observed association persisted in subgroup analysis by gender and body mass index. CONCLUSION: Our results demonstrate that elevated levels of perfluoroalkyl chemicals are associated with hyperuricemia even at low perfluoroalkyl chemical exposure levels as seen in the US general population.				●						-		B	B
1055	ヒト（腎毒性）	C8 Science Panel.	Probable link evaluations for heart disease, kidney disease, liver disease, osteoarthritis and parkinson's disease	2012	C8 probable link reports, http://www.c8sciencepanel.org/prob_link.html	No abstract available						●			C8 science panel ウェブサイト公表資料。対象外とする		D	D
1056	ヒト（呼吸器）	Agier, L.; Basagaña, X.; Maitre, L.; Granum, B.; Bird, P. K.; Casas, M.; Oftedal, B.; Wright, J.; Andrusaityte, S.; de Castro, M.; Cequier, E.; Chatzi, L.; Donaire-Gonzalez, D.; Grazuleviciene, R.; Haug, L. S.; Sakhi, A. K.; Leventakou, V.; Mceachan, R.; Nieuwenhuijsen, M.; Petraviciene, I.; Robinson, O.; Roumeliotaki, T.; Sunyer, J.; Tamayo-Uria, I.; Thomsen, C.; Urquiza, J.; Valentin, A.; Slama, R.; Vrijheid, M.; Siroux, V.	Early-life exposome and lung function in children in Europe: an analysis of data from the longitudinal, population-based HELIX cohort	2019	The Lancet Planetary Health. 2019 Feb;3(2):e81-e92. doi: 10.1016/S2542-5196(19)30010-5. Epub 2019 Feb 6.	BACKGROUND: Several single-exposure studies have documented possible effects of environmental factors on lung function, but none has relied on an exposome approach. We aimed to evaluate the association between a broad range of prenatal and postnatal lifestyle and environmental exposures and lung function in children.METHODS: In this analysis, we used data from 1033 mother-child pairs from the European Human Early-Life Exposome (HELIX) cohort (consisting of six existing longitudinal birth cohorts in France, Greece, Lithuania, Norway, Spain, and the UK of children born between 2003 and 2009) for whom a valid spirometry test was recorded for the child. 85 prenatal and 125 postnatal exposures relating to outdoor, indoor, chemical, and lifestyle factors were assessed, and lung function was measured by spirometry in children at age 44724 years. Two agnostic linear regression methods, a deletion-substitution-addition (DSA) algorithm considering all exposures simultaneously, and an exposome-wide association study (ExWAS) considering exposures independently, were applied to test the association with forced expiratory volume in 1 s percent predicted values (FEV1%). We tested for two-way interaction between exposures and corrected for confounding by co-exposures.FINDINGS: In the 1033 children (median age 8·1 years, IQR 6·5-9·0), mean FEV1% was 98·8% (SD 13·2). In the ExWAS, prenatal perfluorononanoate (p=0·034) and perfluorooctanoate (p=0·030) exposures were associated with lower FEV1%, and inverse distance to nearest road during pregnancy (p=0·030) was associated with higher FEV1%. Nine postnatal exposures were associated with lower FEV1%: copper (p=0·041), ethyl-paraben (p=0·029), five phthalate metabolites (mono-2-ethyl 5-carboxypentyl phthalate [p=0·016], mono-2-ethyl-5-hydroxyhexyl phthalate [p=0·023], mono-2-ethyl-5-oxohexyl phthalate [p=0·0085], mono-4-methyl-7-oxooctyl phthalate [p=0·040], and the sum of di-ethylhexyl phthalate metabolites [p=0·014]), house crowding (p=0·015), and facility density around schools (p=0·027). However, no exposure passed the significance threshold when corrected for multiple testing in ExWAS, and none was selected with the DSA algorithm, including when testing for exposure interactions.INTERPRETATION: Our systematic exposome approach identified several environmental exposures, mainly chemicals, that might be associated with lung function. Reducing exposure to these ubiquitous chemicals could help to prevent the development of chronic respiratory disease.FUNDING: European Community's Seventh Framework Programme (HELIX project).	●	●							-		B	C
1057	ヒト（骨毒性）	Cluett, R.; Seshasayee, S. M.; Rokoff, L. B.; Rifas-Shiman, S. L.; Ye, X.; Calafat, A. M.; Gold, D. R.; Coull, B.; Gordon, C. M.; Rosen, C. J.; Oken, E.; Sagiv, S. K.; Fleisch, A. F.	Per- and Polyfluoroalkyl Substance Plasma Concentrations and Bone Mineral Density in Midchildhood: A Cross-Sectional Study (Project Viva, United States)	2019	Environ Health Perspect 127: 87006. doi: 10.1289/EHP4918. Epub 2019 Aug 21.	BACKGROUND: Identifying factors that impair bone accrual during childhood is a critical step toward osteoporosis prevention. Exposure to per- and polyfluoroalkyl substances (PFASs) has been associated with lower bone mineral density, but data are limited, particularly in children.METHODS: We studied 576 children in Project Viva, a Boston-area cohort of mother/child pairs recruited prenatally from 1999 to 2002 We quantified plasma concentrations of several PFASs and measured areal bone mineral density (aBMD) by dual-energy X-ray absorptiometry (DXA) in midchildhood. We used linear regression to examine associations between plasma concentrations of individual PFASs and aBMD z-score. We used weighted quantile sum (WQS) regression to examine the association of the PFAS mixture with aBMD z-score. All models were adjusted for maternal age, education, annual household income, census tract median household income, and child age, sex, race/ethnicity, dairy intake, physical activity, and year of blood draw.RESULTS: Children were [[Formula: see text]] [Formula: see text] of age. The highest PFAS plasma concentrations were of perfluorooctanesulfonic acid (PFOS) {median [interquartile range (IQR)]: 6.4 -5.6 ng/mL} and perfluorooctanoic acid (PFOA) {median (IQR): 4.4 -3.2 ng/mL]. Using linear regression, children with higher plasma concentrations of PFOA, PFOS, and perfluorodecanoate (PFDA) had lower aBMD z-scores [e.g., [Formula: see text]: [Formula: see text]; 0.95 confidence interval (CI): [Formula: see text], [Formula: see text] per doubling of PFOA]. The PFAS mixture was negatively associated with aBMD z-score ([Formula: see text]: [Formula: see text]; 0.95 CI: [Formula: see text], [Formula: see text] per IQR increment of the mixture index).CONCLUSIONS: PFAS exposure may impair bone accrual in childhood and peak bone mass, an important determinant of lifelong skeletal health.	●	●							-		B	B
1058	ヒト（その他）	Etzel, T. M.; Braun, J. M.; Buckley, J. P.	Associations of serum perfluoroalkyl substance and vitamin D biomarker concentrations in NHANES, 2003-2010	2019	Int J Hyg Environ Health. 2019 Mar;222(2):262-269. doi: 10.1016/j.ijheh.2018.11.003. Epub 2018 Nov 28.	Perfluoroalkyl substances (PFAS) are persistent endocrine disrupting chemicals found in industrial and commercial products. Previous research has shown that other endocrine disrupting chemicals such as phthalates and bisphenol A may alter circulating levels of vitamin D; however, no research has examined associations between PFAS and vitamin D biomarkers. We conducted a cross-sectional analysis of 7040 individuals aged 12 years and older participating in the 2003-2010 cycles of the United States National Health and Nutrition Examination Survey (NHANES). Concentrations of perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorohexane sulfonic acid (PFHxS), perfluorononanoic acid (PFNA), and total 25-hydroxyvitamin D [25(OH)D] were measured in serum samples. We used multivariable linear regression to estimate covariate-adjusted differences in total 25(OH)D or prevalence odds of vitamin D deficiency per log2 change in PFAS concentrations. We also assessed potential effect measure modification by gender, age, and race/ethnicity. PFAS were detected in over 0.98 of the samples. In adjusted models, each 2-fold increase in PFOS was associated with 0.9 nmol/L (95% CI: 0.2, 1.5) lower total 25(OH)D concentrations, with associations significantly stronger among whites (β: -1.7; 0.95 CI: -2.6, -0.7) and individuals older than 60 years of age (β: -1.7; 0.95 CI: -2.9, -0.5). Each 2-fold increase in PFHxS was associated with 0.8 nmol/L (95% CI: 0.3, 1.3) higher total 25(OH)D, and this association was not modified by age, gender, and race/ethnicity. PFOA and PFNA were not associated with total 25(OH)D. When assessing prevalence odds of vitamin D deficiency, we observed similar patterns of association with PFAS concentrations. Our results suggest that some PFAS may be associated with altered vitamin D levels in the United States population, and associations may vary by chemical, age, and race/ethnicity. Prospective epidemiological studies are needed to confirm our findings and determine their implications for vitamin D-associated health outcomes in children and adults.	●	●							-	1	A	B
1059	ヒト（呼吸器）	Gaylord, A.; Berger, K. I.; Naidu, M.; Attina, T. M.; Gilbert, J.; Koshy, T. T.; Han, X.; Marmor, M.; Shao, Y.; Giusti, R.; Goldring, R. M.; Kannan, K.; Trasande, L.	Serum perfluoroalkyl substances and lung function in adolescents exposed to the World Trade Center disaster	2019	Environ Res. 2019 May;172:266-272. doi: 10.1016/j.envres.2019.02.024. Epub 2019 Feb 16.	The effects of childhood exposure to perfluoroalkyl substances (PFASs) on lung function remain mostly unknown. Previous research indicates that children living or going to school near the World Trade Center (WTC) disaster were exposed to high levels of PFASs, among other toxic chemicals. To explore the effects of PFAS exposure on lung function, we measured serum PFASs in a cohort of children from the WTC Health Registry and a matched control group. Perfluorooctanesulfonate had the highest median concentrations in both groups (WTCHR = 3.72 ng/mL, Comparison = 2.75 ng/mL), while the lowest median concentrations were seen for perfluoroundecanoic acid (WTCHR = 0.12 ng/mL, Comparison = 0.01 ng/mL). Lung function outcomes were measured by spirometry, plethysmography, and oscillometry. Asthma diagnosis and serum eosinophil count were also recorded. We examined the relationships of each PFAS with lung function parameters and eosinophil count using linear regressions. Odds ratios for asthma were obtained for each PFAS using logistic regression. The effect of total PFASs on these outcomes was also assessed. All regression models were adjusted for sex, race/ethnicity, age, body mass index (BMI) and tobacco smoke exposure. We found that serum PFASs were not statistically associated with the measured lung function parameters, asthma diagnosis, or eosinophil count in this cohort (p < 0.05). These findings highlight the need for more longitudinal studies to explore the long-term effects of childhood PFAS exposure on lung function past adolescence and early adulthood.	●	●							-		C	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ラン①C	文献ラン②C
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1060	ヒト（消化管毒性）	Hammer, T.; Lophaven, S. N.; Nielsen, K. R.; Petersen, M. S.; Munkholm, P.; Weihe, P.; Burisch, J.; Lynge, E.	Dietary risk factors for inflammatory bowel diseases in a high-risk population: Results from the Faroese IBD study	2019	United European Gastroenterol J.;7(7):924-932. doi: 10.1177/2050640619852244. Epub 2019 May 19.	BACKGROUND: The Faroe Islands currently have the highest recorded inflammatory bowel disease (IBD) incidence in the world. OBJECTIVE: This study investigated environmental risk factors for IBD in the Faroese population. METHODS: Environmental exposure data including lifestyle risk factors and neurotoxicants collected for over 30 years were retrieved from the Children's Health and the Environment in the Faroes (CHEF) cohorts including mainly mother-child pairs, with exposure data collected from pregnant mothers. For lifestyle risk factors, the incidence of IBD and ulcerative colitis (UC) was calculated as the rate ratio (RR) with 0.95 confidence intervals (CI) in exposed versus non-exposed persons. For neurotoxicants RR was calculated for persons with high versus low exposure. RESULTS: Six cohorts included 5698 persons with complete follow-up data and at least one exposure, and 37 were diagnosed with IBD. For pilot whale/blubber, the RR was 1.02 (95% CI, 0.48-2.18); RR of 1.01 for fish (95% CI, 0.35-2.91); and of the pollutants studied, a statistical significantly increased risk was found for 1,1,1,-trichloro-2,2-bis-(p-chlorophenyl) ethane (p,p'-DDT); RR 3.04 (95% CI, 1.12-8.30). RRs were 1.96 (95% CI, 1.03-3.73) for smoking and 1.1 (95% CI, 0.55-2.19) for alcohol intake. CONCLUSION: The high IBD incidence is unlikely to be caused by special dietary habits or by environmental pollutants.	●	●							-		C	C
1061	ヒト（その他）	Hu, Y.; Liu, G.; Rood, J.; Liang, L.; Bray, G. A.; de Jonge, L.; Coull, B.; Furtado, J. D.; Qi, L.; Grandjean, P.; Sun, Q.	Perfluoroalkyl substances and changes in bone mineral density: A prospective analysis in the POUNDS-LOST study	2019	Environ Res. 2019 Dec;179(Pt A):108775. doi: 10.1016/j.envres.2019.108775. Epub 2019 Sep 27.	BACKGROUND: Recent studies suggested an inverse association between exposures to perfluoroalkyl substances (PFASs) and bone mineral density (BMD). Whether exposures to PFASs are also associated with changes in BMD has not been examined.METHODS: Five major PFASs (perfluorooctanesulfonic acid, PFOS; perfluorooctanoic acid, PFOA; perfluorohexanesulfonic acid, PFHxS; perfluorononanoic acid, PFNA; perfluorodecanoic acid, PFDA) and BMD (g/cm2) at six bone sites (spine, total hip, femoral neck, hip intertrochanteric area, hip trochanter, and hip Ward's triangle area) were measured at baseline among 294 participants in the POUNDS-LOST study, a weight-loss trial, of whom a total of 175 participants had BMD measured at both baseline and year 2 Linear regression was used to model the differences or changes in BMD for each SD increment of PFAS concentrations. In a secondary analysis, interactions between PFASs and baseline body mass index (BMI), as well as a BMI-related genetic risk score (GRS) derived from 97 BMI-predicting SNPs were examined in relation to changes in BMD.RESULTS: At baseline, both PFOS and PFOA were significantly associated with lower BMD at several sites. For each SD increase of PFOS, the βs (95% CIs) for BMD were -0.020(-0.037, -0.003) for spine, -0.013(-0.026, 0.001) for total hip, -0.014(-0.028, 0.000) for femoral neck, and -0.013(-0.026, 0.000) for hip trochanter. For PFOA, the corresponding figures were -0.021(-0.038, -0.004) for spine, -0.015(-0.029, -0.001) for total hip, and -0.015(-0.029, -0.002) for femoral neck. After adjusting for baseline covariates and 2-year weight change, higher baseline plasma concentrations of PFOS, PFNA, and PFDA were associated with greater reduction in BMD in the hip; the βs (95% CIs) were -0.005(-0.009, -0.001), -0.006(-0.010, -0.001), and -0.005(-0.009, -0.001), respectively. Similar associations were found in hip intertrochanteric area for all PFASs except PFHxS, with βs ranging from -0.006 for PFOA to -0.008 for PFOS and PFNA. Participants with a higher GRS tended to have less PFAS-related BMD decline in total hip (Pinteraction = 0.005) and the hip intertrochanteric area (Pinteraction = 0.021). There were similar PFAS-related BMD changes by baseline BMI levels, although the interactions did not achieve statistical significance.CONCLUSIONS: This study demonstrated that higher plasma PFAS concentrations were not only associated with a lower BMD at baseline, but also a faster BMD loss in a weight-loss trial setting. Genetic predisposition to larger body size may somewhat attenuate the deleterious effects of PFASs on BMD. Further exploration of the possible impact of PFAS exposures on bone density is warranted.	●	●							-	1	A	B
1062	ヒト（血液毒性）	Jain, R. B.	Associations between selected perfluoroalkyl acids in serum and hemoglobin in whole blood, a biomarker of anemia: Impact of deteriorating kidney function	2020	Environ Pollut 263: 114458. doi: 10.1016/j.envpol.2020.114458. Epub 2020 Mar 31.	Data (N = 11251) from National Health and Nutrition Examination Survey (NHANES) for 2003-2016 for US adults aged ≥20 years were stratified by gender and anemia and analyzed to evaluate the associations between the concentrations of whole blood hemoglobin (WBHGB) and selected perfluoroalkyl acids (PFAAs) in serum by stages of glomerular filtration (GF). Investigated PFAAs were perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorodecanoic acid (PFDA), perfluorohexane sulfonic acid (PFHxS), and perfluorononanoic acid (PFNA). Females with whole blood hemoglobin concentrations <12 g/dL and males with whole blood hemoglobin concentrations <13 g/dL were classified as being anemic. Regression models with log10 transformed concentrations of whole blood hemoglobin as dependent variable and age, poverty income ratio, body mass index, serum cotinine, daily alcohol intake, survey year, and log10 concentrations of one of the PFAA as independent variables were fitted. For anemic females, association between WBHGB and PFAA concentrations were uniformly positive across worsening stages of renal failure and percent increases for 0.1 increases in PFAAs varied between 0.0003 and 0.39%. For anemic males, association between WBHGB and PFAA concentrations were positive except at GF-3A (45 ≤ eGFR<60 mL/min/1.73 m2) and percent increases for 0.1 increases in PFAAs varied between 0.0002 and 0.53%. Thus, more often than not, presence of positive associations between WBHGB and PFAA among anemics imply elevated levels of PFAA are associated with higher levels of WBHGB. Similar results were observed for non-anemic males and females, however strengths of associations between whole blood hemoglobin and PFAAs were several fold higher among anemic compared to non-anemic participants. Hemoglobin is consistently associated with serum PFAAs.	●	●							-		B	B
1063	ヒト（骨毒性）	Khalil, N.; Chen, A.; Lee, M.; Czerwinski, S. A.; Ebert, J. R.; Dewitt, J. C.; Kannan, K.	Association of Perfluoroalkyl Substances, Bone Mineral Density, and Osteoporosis in the US Population in NHANES 2009-2010	2016	Environ Health Perspect. 2016 Jan;124(1):81-7. doi: 10.1289/ehp.1307909. Epub 2015 Jun 9.	BACKGROUND: Perfluoroalkyl substances (PFASs), including perfluorooctanoic acid (PFOA), perfluoro-octane sulfonic acid (PFOS), perfluorohexane sulfonic acid (PFHxS), and perfluorononanoic acid (PFNA), are detectable in the serum of 0.95 of the U.S. population.	●	●	●	●					-		D	B
1064	ヒト（骨毒性）	Koskela, A.; Koponen, J.; Lehenkari, P.; Viluksela, M.; Korkalainen, M.; Tuukkanen, J.	Perfluoroalkyl substances in human bone: concentrations in bones and effects on bone cell differentiation	2017	Sci Rep. 2017 Jul 28;7(1):6841. doi: 10.1038/s41598-017-07359-6.	Perfluoroalkyl substances (PFAS), including two most commonly studied compounds perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA), are widely distributed environmental pollutants, used extensively earlier. Due to their toxicological effects the use of PFAS is now regulated. Based on earlier studies on PFOA's distribution in bone and bone marrow in mice, we investigated PFAS levels and their possible link to bone microarchitecture of human femoral bone samples (n = 18). Soft tissue and bone biopsies were also taken from a 49-year old female cadaver for PFAS analyses. We also studied how PFOA exposure affects differentiation of human osteoblasts and osteoclasts. PFAS were detectable from all dry bone and bone marrow samples, PFOS and PFOA being the most prominent. In cadaver biopsies, lungs and liver contained the highest concentrations of PFAS, whereas PFAS were absent in bone marrow. Perfluorononanoic acid (PFNA) was present in the bones, PFOA and PFOS were absent. In vitro results showed no disturbance in osteogenic differentiation after PFOA exposure, but in osteoclasts, lower concentrations led to increased resorption, which eventually dropped to zero after increase in PFOA concentration. In conclusion, PFAS are present in bone and have the potential to affect human bone cells partly at environmentally relevant concentrations.	●	●							-		C	B
1065	ヒト（骨毒性）	Lin, L. Y.; Wen, L. L.; Su, T. C.; Chen, P. C.; Lin, C. Y.	Negative association between serum perfluorooctane sulfate concentration and bone mineral density in US premenopausal women: NHANES, 2005-2008	2014	J Clin Endocrinol Metab 99: 2173-2180. doi: 10.1210/jc.2013-3409. Epub 2014 Feb 28.	CONTEXT: Perfluorooctanoic acid (PFOA) and perfluorooctane sulfate (PFOS) are used in a variety of products worldwide. However, the relationship among serum PFOA, PFOS concentration, bone mineral density (BMD), and the risk of fractures has never been addressed.OBJECTIVES: The study examined the association among serum PFOA, PFOS concentration, and lumbar spine and total hip BMD in the general US population.DESIGN AND PARTICIPANTS: We analyzed data on 2339 adults (aged ≥20 y) from the National Health and Nutrition Examination Survey conducted in 2005-2006 and 2007-2008 to determine the relationship among serum PFOA, PFOS concentration, and total lumbar spine and total hip BMD measured by dual-energy x-ray absorptiometry and history of fractures cross-sectionally.RESULTS: After weighting for sampling strategy, a 1-U increase in the natural log-transformed serum PFOS level was associated with a decrease in total lumbar spine BMD by 0.022 g/cm(2) (95% confidence interval -0.038, -0.007; P = .006) in women not in menopause. There was no association among PFOA, PFOS concentration, and self-reported fracture in adults.CONCLUSION: Serum PFOS concentration is associated with decreased total lumbar spine BMD in women not in menopause. However, the potential biological significance of this effect is marginal and subclinical in the general US population. Further studies are warranted to clarify the causal relationship between perfluorinated chemical exposure and BMD.	●	●		●					-		C	B
1066	ヒト（虫歯）	Puttige Ramesh, N.; Arora, M.; Braun, J. M.	Cross-sectional study of the association between serum perfluorinated alkyl acid concentrations and dental caries among US adolescents (NHANES 1999-2012)	2019	BMJ Open. 2019 Feb 19;9(2):e024189. doi: 10.1136/bmjopen-2018-024189.	STUDY OBJECTIVES: Perfluoroalkyl acids (PFAAs) are a class of anthropogenic and persistent compounds that may impact some biological pathways related to oral health. The objective of our study was to estimate the relationship between dental caries prevalence and exposure to four PFAA: perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorohexane sulfonic acid (PFHxS) and perfluorooctane sulfonic acid (PFOS) in a nationally representative sample of US adolescents.SETTING/DESIGN: We analysed cross-sectional data from the National Health and Nutrition Examination Survey from 1999 to 2012 for 12-19-year-old US adolescents.PARTICIPANTS: Of 10 856 adolescents aged 12 to 19 years who had a dental examination, we included 2869 with laboratory measurements for serum PFAA concentrations and complete covariate data in our study.PRIMARY AND SECONDARY OUTCOME MEASURES: Dental caries prevalence was defined as the presence of decay or a restoration on any tooth surface, or the loss of a tooth due to tooth decay. We used multivariable logistic regression to estimate the covariate-adjusted association between serum PFAA concentrations and dental caries prevalence, accounting for the complex National Health and Nutrition Examination Survey design.RESULTS: Of 2869 adolescents, 0.59 had one or more dental caries. We observed no associations between the prevalence of dental caries and serum concentrations of PFOA, PFOS or PFHxS. The adjusted odds of caries were 0.21 (OR 0.79; 0.95 CI 0.63 to 1.01), 0.15 (OR 0.85; 0.95 CI 0.67 to 1.08) and 0.3 (OR 0.7; 0.95 CI 0.55 to 0.90) lower among adolescents in the 2nd, 3rd and 4th serum PFNA concentration quartiles compared to adolescents in the first quartile, respectively. The linear trend for this association was not statistically significant.CONCLUSION: PFOA, PFOS and PFHxS were not associated with prevalence of dental caries. The prevalence of caries was reduced with increasing serum PFNA concentrations; however, these results should be interpreted cautiously given that we were unable to adjust for several factors related to oral health.	●	●							-		C	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ラン①B	文献ラン②B
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1067	ヒト（骨毒性）	Uhl, S. A.; James-Todd, T.; Bell, M. L.	Association of Osteoarthritis with Perfluorooctanoate and Perfluorooctane Sulfonate in NHANES 2003-2008	2013	Environ Health Perspect. 2013 Apr;121(4):447-52. doi: 10.1289/ehp.1205673. Epub 2013 Feb 14.	BACKGROUND: Perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) are persistent, synthetic industrial chemicals. Perfluorinated compounds are linked to health impacts that may be relevant to osteoarthritis, cartilage repair, and inflammatory responses.OBJECTIVES: We investigated whether PFOA and PFOS exposures are associated with prevalence of osteoarthritis, and whether associations differ between men and women.METHODS: We used multiple logistic regression to estimate associations between serum PFOA and PFOS concentrations and self-reported diagnosis of osteoarthritis in persons 20-84 years of age who participated in NHANES during 2003-2008. We adjusted for potential confounders including age, income, and race/ethnicity. Effects by sex were estimated using stratified models and interaction terms.RESULTS: Those in the highest exposure quartile had higher odds of osteoarthritis compared with those in the lowest quartile [odds ratio (OR) for PFOA = 1.55; 0.95 CI: 0.99, 2.43; OR for PFOS = 1.77; 0.95 CI: 1.05, 2.96]. When stratifying by sex, we found positive associations for women, but not men. Women in the highest quartiles of PFOA and PFOS exposure had higher odds of osteoarthritis compared with those in the lowest quartiles (OR for PFOA = 1.98; 0.95 CI: 1.24, 3.19 and OR for PFOS = 1.73; 0.95 CI: 0.97, 3.10).CONCLUSIONS: Higher concentrations of serum PFOA were associated with osteoarthritis in women, but not men. PFOS was also associated with osteoarthritis in women only, though effect estimates for women were not significant. More research is needed to clarify potential differences in susceptibility between women and men with regard to possible effects of these and other endocrine-disrupting chemicals.	●	●		●					-		B	B
1068	ヒト（虫歯）	Wiener, R. C.; Waters, C.	Perfluoroalkyls/polyfluoroalkyl substances and dental caries experience in children, ages 3-11 years, National Health and Nutrition Examination Survey, 2013-2014	2019	J Public Health Dent. 2019 Dec;79(4):307-319. doi: 10.1111/jphd.12329. Epub 2019 Jul 8.	OBJECTIVE: The objective of this research is to determine the association of seven perfluoroalkyl and polyfluoroalkyl substances versus dental caries experience in US children, ages 3-11 years.METHODS: A cross-sectional study design was used in the analysis of National Health and Nutrition Examination Survey 2013-2014 serological data of perfluoroalkyl and polyfluoroalkyl substances. The seven perfluoroalkyl and polyfluoroalkyl substances were: 2-(N-methyl-perfluorooctane sulfonamide) acetic acid; perfluorodecanoic acid; perfluorononanoic acid; perfluorohexane sulfonic acid; linear isomers of perfluorooctanoate; linear perfluorooctane sulfonate; and monomethyl branched isomers of perfluorooctane sulfonate. Two summative variables were created: monomethyl branch isomers of perfluorooctane sulfonic acid with linear isomer of perfluorooctane and branch isomers of perfluorooctanoate with linear isomer perfluorooctonate.RESULTS: In unadjusted logistic regression, in which the comparison was between the less than 75th percentile reference group and the 75th and above percentile group, higher perfluorodecanoic acid was associated with dental caries experience [unadjusted odds ratio: 1.79 (95% CI: 1.19, 2.46; P = 0.0069); adjusted odds ratio: 1.54 (95% CI: 1.03, 2.30; P = 0.0385)].CONCLUSIONS: Of the seven examined perfluoroalkyl and polyfluoroalkyl substances, only perfluorodecanoic acid had an association with dental caries experience in an unadjusted model and adjusted logistic regression model.	●	●							-		C	B
1069	ヒト（消化管毒性）	Xu, Y.; Li, Y.; Scott, K.; Lindh, C. H.; Jakobsson, K.; Fletcher, T.; Ohlsson, B.; Andersson, E. M.	Inflammatory bowel disease and biomarkers of gut inflammation and permeability in a community with high exposure to perfluoroalkyl substances through drinking water	2020	Environ Res. 2020 Feb;181:108923. doi: 10.1016/j.envres.2019.108923. Epub 2019 Nov 14.	Perfluoroalkyl substances (PFAS) can act as surfactants and have been suggested to be capable of affecting gut mucosa integrity, a possible factor in the pathogenesis of inflammatory bowel disease (IBD). So far, only PFOA has been shown to have a positive association with ulcerative colitis. The present study aimed to investigate the association of PFAS and clinically diagnosed IBD in the Ronneby cohort, a population with high PFAS exposure (especially high PFOS and PFHxS) from Aqueous Film-Forming Foam through drinking water, using registry data. Additionally, to explore associations of PFAS with fecal zonulin and calprotectin, subclinical biomarkers of gut inflammation and permeability, in a sub-set of participants from Ronneby and Karlshamn (a nearby control municipality). The registry study included all people that ever resided in Ronneby municipality at least one year between 1980 and 2013 Yearly exposure to contaminated drinking water was assessed based on residential addresses and waterworks supply data, and the population classified by early, mid and late periods in ascending level of contamination. Diagnosed IBD cases were retrieved from the Swedish National Patient register and cause-of-death register. The Cox proportional hazards model was used to derive the hazard ratios (HRs) for diagnosed IBD. The biomarker study included 189 individuals who provided fecal samples. Serum PFAS were measured using LC-MS/MS. Fecal zonulin and calprotectin were measured using ELISA. Linear regression was used to assess the associations between measured PFAS and biomarker levels. In the registry study, no raised HRs for diagnosed IBD were found for cohort subjects with mid (1995-2004) or late period (2005-2013) exposure compared to never exposure. Early period exposure only (1985-1994) showed raised HRs for Crohn's disease (HR = 1.58, p = 0.048) and other non-specified IBD (HR = 1.38, p = 0.037). In the biomarker study, Karlshamn showed higher fecal calprotectin levels (median = 99.6 mg/kg in Karlshamn vs. 66.8 mg/kg in Ronneby, p = 0.04). A trend of decreased calprotectin with increased serum PFAS indicated higher PFAS was associated with lower degree of gut inflammation (p = 0.002). No association between serum PFAS and fecal zonulin was found. In conclusion, the present study found no consistent evidence to support PFAS exposure as a risk factor for IBD.	●	●							-		B	B
1070	ヒト（視覚器）	Zeeshan, M.; Yang, Y.; Zhou, Y.; Huang, W.; Wang, Z.; Zeng, X. Y.; Liu, R. Q.; Yang, B. Y.; Hu, L. W.; Zeng, X. W.; Sun, X.; Yu, Y.; Dong, G. H.	Incidence of ocular conditions associated with perfluoroalkyl substances exposure: Isomers of C8 Health Project in China	2020	Environ Int 137: 105555. doi: 10.1016/j.envint.2020.105555. Epub 2020 Feb 18.	The detrimental effects of perfluoroalkyl substances (PFASs) on several physiological systems have been reported, but the association of PFASs with eye, one of the most sensitive and exposed organ, has never been explored. To investigate the association between eye diseases including visual impairment (VI) and PFASs isomers, a cross-sectional stratified study was conducted in 1202 Chinese population, aged 22-96 years, from Shenyang, China. A standard protocol including Snellen vision chart, slit-lamp microscopy and direct ophthalmoscopy was used to examine eye diseases/conditions relating to anterior and posterior segment of eyes. In addition, we measured the blood concentrations of 19 linear and branched PFASs at one-time point. Results indicated that blood levels of PFASs were significantly higher in eye disease group than normal group. PFASs exposure were positively associated with both combined eye diseases and individual eye diseases. Among other PFASs, linear perfluorooctane sulfonate (n-PFOS; odds ratio [OR] = 3.37, 0.95 confidence interval [CI]: 2.50, 4.56), branched perfluorooctane sulfonate (Br-PFOS; OR = 2.25, 0.95 CI: 1.72, 2.93) and linear perfluorooctanoic acid (n-PFOA; OR = 1.79, 0.95 CI: 1.36, 2.37) significantly increases the odds of VI. Vitreous disorder was adversely associated with long-chain PFASs exposure. For example, perfluorotridecanoic acid (PFTrDA; OR = 1.86, 0.95 CI: 1.51, 2.29) and perfluorodecanoic acid (PFDA; OR = 1.79, 0.95 CI: 1.36, 2.36) showed the most significant association. In conclusion, this study suggests higher serum PFASs levels were associated with increase odds of VI and vitreous disorder in Chinese adults.	●	●							-		B	B
1071	ヒト（骨毒性）	Innes, Kim E; Ducatman, Alan M; Luster, Michael I; Shankar, Anoop	Association of osteoarthritis with serum levels of the environmental contaminants perfluorooctanoate and perfluorooctane sulfonate in a large Appalachian population	2011	Am J Epidemiol. 2011 Aug 15;174(4):440-50. doi: 10.1093/aje/kwr107. Epub 2011 Jun 27.	Perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) are persistent environmental contaminants that affect metabolic regulation, inflammation, and other factors implicated in the pathogenesis of osteoarthritis (OA). However, the link between these compounds and OA remains unknown. In this study, the authors investigated the association of OA with PFOA and PFOS in a population of 49,432 adults from 6 PFOA-contaminated water districts in the mid-Ohio Valley (2005-2006). Participants completed a comprehensive health survey; serum levels of PFOA, PFOS, and a range of other blood markers were also measured. Medical history, including physician diagnosis of osteoarthritis, was assessed via self-report. Analyses included adjustment for demographic and lifestyle characteristics, body mass index, and other potential confounders. Reported OA showed a significant positive association with PFOA serum levels (for highest quartile of PFOA vs. lowest, adjusted odds ratio = 1.3, 95% confidence interval: 1.2, 1.5; P-trend = 0.00001) and a significant inverse association with PFOS (for highest quartile vs. lowest, adjusted odds ratio = 0.8, 95% confidence interval: 0.7, 0.9; P-trend = 0.00005). The relation between PFOA and OA was significantly stronger in younger and nonobese adults. Although the cross-sectional nature of this large, population-based study limits causal inference, the observed strong, divergent associations of reported OA with PFOA and PFOS may have important public health and etiologic implications and warrant further investigation.				●					-		B	B
1072	ヒト（その他）	MacPherson, I. R.; Bissett, D.; Petty, R. D.	A first-in-human phase I clinical trial of CXR1002 in patients (pts) with advanced cancer	2011	J Clin Oncol 29(15_suppl), doi: 10.1200/jco.2011.29.15_suppl.3063	Background: CXR1002, an ammonium salt of perfluorooctanoic acid, is a lipid mimetic that causes ER stress and inhibits PIM kinases. Aims of this study were to assess the tolerability, safety and pharmacokinetics (PK) and to identify the recommended phase II dose (RP2D) of CXR1002 administered orally once weekly. Methods: Sequential cohorts of pts with advanced refractory solid tumors were enrolled. Cohort 1 received a single dose of CXR1002 followed by once weekly dosing commenced 6 weeks (wks) later. Subsequent cohorts received CXR1002 once wkly. Dose escalation followed a standard 3+3 design until dose-limiting toxicity (DLT) was observed in ≥ 2/6 pts. Plasma levels of CXR1002 were determined by LC-MS/MS at the following time-points: pre-dose, 2, 3, 4, 24 hours post-dose for the first 6 wks then 6 wkly. Exploratory PD analyses included: serum leptin; plasma lipids, glucose and insulin. Results: 41 pts have been enrolled (23M / 18F); median age 63 (range 36-75); PS < 2; colorectal (n=16); pancreatic (n=5); other (n=20). CXR1002 was administered at 10 dose levels [mg (pts entered/evaluable)]: 50 (4/3), 100 (3/3), 200 (3/3), 300 (4/3), 450 (3/3), 600 (8/6), 750 (3/3), 950 (4/3), 1000 (3/3), 1200 (6/6). Median duration of therapy was 6.5 wks (range 0-40). DLT (grade 5 renal failure / grade 4 transaminitis; possibly drug-related) occurred in 1 pt at the 600mg dose. Protocol-defined MTD was not reached and the RP2D of 1,000mg wkly was based on tolerability of common cumulative drug-related toxicities, primarily: fatigue, nausea, vomiting, and diarrhea. Cmax was reached 1.5 hours after administration of a single dose of CXR1002 and maintained at a constant level over a 6 wk sampling period. CXR1002 was cumulative with wkly dosing with increased exposure seen with increasing dose level and duration. Reductions in LDL-cholesterol consistent with a PD effect were observed. Stable disease >12 wks was observed in 8 pts including pts with anaplastic thyroid (40 wks), pancreatic (35 wks), and cervical cancer (34 wks). Conclusions: The RP2D of CXR1002 when administered orally once wkly is 1,000mg. An expansion phase at this dose level will investigate biomarkers of PIM kinase inhibition. CXR1002 exhibits unusual PK with an extremely long t1/2.				●			●		-		C	A
1073	ヒト（血液毒性）	Olsen, G. W.; Burris, J. M.; Burlew, M. M.; Mandel, J. H.	An epidemiologic investigation of clinical chemistries, hematology and hormones in relation to serum levels of perfluorooctane sulfonate in male fluorochemical production employees	1998	St. Paul, MN: 3M Company. AR226-0030.	No abstract available				●					企業データ		D	D
1074	疫学調査	Little Hocking Water Association	GAC filter C-8 sampling result summary	2010	Little Hocking Water Association, Little Hocking, OH 45742, U.S.	No abstract available					●				企業データ		D	D

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献①ラン	文献②ラン
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1075	実験動物（刺激性）	Biesemeier, JA; Harris, DL	Eye and skin irritation report on sample T-1117(Project No. 4102871)	1974	Madison, WI: WARF Institute Inc.	No abstract available	●				●		●			企業データ		D	D
1076	実験動物（急性毒性）	Cheng, X.; Klaassen, C. D.	Critical role of PPAR-alpha in perfluorooctanoic acid- and perfluorodecanoic acid-induced downregulation of Oatp uptake transporters in mouse livers	2008	Toxicol Sci. 2008 Nov;106(1):37-45. doi: 10.1093/toxsci/kfn161. Epub 2008 Aug 14.	Perfluorooctanoic acid (PFOA) and perfluorodecanoic acid (PFDA) have been detected globally in wildlife and humans. Data from a gene array indicate that PFOA decreases organic anion transporting polypeptides (Oatps) in liver. Na(+)-taurocholate cotransporting polypeptide (Ntcp) and Oatp1a1, 1a4, and 1b2 are major transporters responsible for uptake of bile acids (BAs) and other organic compounds into liver. The purpose of the present study was to determine the effects of two perfluorinated fatty acids, PFOA and PFDA, on mRNA and protein expression of hepatic uptake transporters Oatps and Ntcp, and to determine the underlying regulatory mechanisms by using peroxisome proliferator-activated receptor alpha (PPAR-alpha), constitutive androstane receptor, pregnane-X receptor, NF-E2-related factor 2, and farnesoid X receptor-null mouse models. After 2 days following a single i.p. administration, PFOA did not alter serum BA concentrations, but PFDA increased serum BA concentrations 300%. Furthermore, PFOA decreased mRNA and protein expression of Oatp1a1, 1a4, and 1b2, but not Ntcp in mouse liver. In contrast, PFDA decreased mRNA and protein expression of all four transporters, and decreased the mRNA expression in a dose-dependent manner, with the decrease of Oatp1a4 occurring at lower doses than the other three transporters. Multiple mechanisms are likely involved in the down-regulation of mouse Oatps and Ntcp by PFDA. By using the various transcription factor-null mice, PPAR-alpha was shown to play a central role in the down-regulation of Oatp1a1, 1a4, 1b2, and Ntcp by PFDA. The current studies provide important insight into understanding the mechanisms by which PFDA regulate the expression of hepatic uptake transporters. In conclusion, PFOA and PFDA decrease mouse liver uptake transporters primarily via activation of PPAR-alpha.	●	●	●	●						-		B	B
1077	実験動物（急性毒性）	Dean, W. P.; Jessup, D. C.; Thompson, G.; Romig, G.; Powell, D.	Fluorad Fluorochemical Surfactant FC-95 Acute Oral Toxicity (LD50) Study in Rats	1978	International Research and Development Corporation.	No abstract available	●	●					●			企業データ		D	D
1078	実験動物（眼刺激性）	Gabriel, K.	Primary eye irritation study in rabbits, Report 226-0422	1976	Report 226-0422. Biosearch, Inc.	No abstract available	●	●								企業データ		D	D
1079	実験動物（経皮毒性）	Kennedy, G L Jr	Dermal toxicity of ammonium perfluorooctanoate	1985	Toxicol Appl Pharmacol. 1985 Nov;81(2):348-55. doi: 10.1016/0041-008x(85)90172-3.	Ammonium perfluorooctanoate (CAS Registry No. 3825-26-2) is used commercially in the aqueous polymerization of fluorinated monomers. Because the chemical exists as a fine white powder which can come in contact with skin, its dermal toxicology was studied in rabbits and rats. Dermal applications of 0.5 g for 24 hr produced mild irritation to rabbit skin. The dermal LD50 was 4300 mg/kg for rabbits, 7000 mg/kg for male rats, and greater than 7500 mg/kg for female rats. Rat skin showed less irritation than rabbit skin and the general effects were more pronounced for the male (compared to the female) rat. Subchronic dermal treatment (10 applications, 5 doses, 2 rest days, 5 doses) with either 0, 20, 200, or 2000 mg/kg resulted in no, no, mild, or marked decreases in body weights, respectively. Increases in serum enzyme activities indicating hepatic effects occurred in treated rats. Liver weights were increased and necrosis and enlargement of hepatocytes were microscopically observed. Rats in the 2000 mg/kg-dose group also had epidermal necrosis at the application site. Blood organofluorine amounts were increased in a dose-related manner. All of the treatment-related toxicity findings resolved during a 42-day recovery period although prior exposure was evident by the presence of organofluorine in the blood.	●	●		●		●			●	-		C	B
1080	実験動物（急性毒性）	Maher, Jonathan M; Aleksunes, Lauren M; Dieter, Matthew Z; Tanaka, Yuji; Peters, Jeffrey M; Manautou, Jose E; Klaassen, Curtis D	Nrf2- and PPAR alpha-mediated regulation of hepatic Mrp transporters after exposure to perfluorooctanoic acid and perfluorodecanoic acid	2008	Toxicol Sci. 2008 Dec;106(2):319-28. doi: 10.1093/toxsci/kfn177. Epub 2008 Aug 29.	Perfluorooctanoic acid and perfluorodecanoic acid (PFDA) are commonly used as emulsifiers and surfactants in fluoropolymer manufacturing and are known peroxisome proliferator-activated receptor alpha (PPAR alpha) agonists. PPAR alpha activation induces beta- and omega-oxidation enzymes such as Cyp4a14 and acyl-CoA oxidase, which are a likely cause of subsequent oxidative stress and peroxisome proliferation. Conversely, NF-E2-related factor-2 (Nrf2) is a transcription factor that protects against oxidative stress and inflammation by regulating several detoxification and xenobiotic transporter genes. Because PFDA markedly induces hepatic metabolism and oxidative stress, we hypothesized that PFDA exposure would increase expression of hepatic efflux multidrug resistance-associated protein (Mrp) transporters. A single PFDA dose (80 mg/kg) administered to mice increased hepatic Mrp3 (fourfold) and Mrp4 (31-fold) mRNA expression. Upregulation of Mrp3 and Mrp4 correlated with elevated serum-conjugated bilirubin and bile acids, respectively. To determine the mechanism of Mrp3 and Mrp4 induction, PFDA was administered to Nrf2-null mice, PPAR alpha-null mice, and mice pretreated with gadolinium chloride, a Kupffer cell-depleting chemical capable of inhibiting the inflammatory cytokine response. In both PPAR alpha- and Nrf2-null mice, maximal induction of Mrp3 and Mrp4 mRNA after PFDA administration was attenuated. Gadolinium chloride pretreatment reduced serum and hepatic tumor necrosis factor-alpha levels after PFDA treatment, as well as Mrp4 mRNA expression by 30%, suggesting that Kupffer cell-derived mediators may contribute to Mrp induction. Thus, after PFDA administration, the liver mounts a compensatory hepatoprotective response via PPAR alpha and Nrf2, markedly increasing Mrp3 and Mrp4 expression, with corresponding increases in serum of known Mrp3 and Mrp4 substrates.	●	●	●	●						-		B	C
1081	実験動物（急性毒性）	Rusch, G. M.	An Acute Inhalation Toxicity Study of T-2307 CoC in the Rat	1979	3M-EPA-0029829. Rusch, GM.	No abstract available	●	●								企業データ		D	D
1082	実験動物（急性毒性）	Adinehzadeh, M; Reo, N V; Jarnot, B M; Taylor, C A; Mattie, D R	Dose-response hepatotoxicity of the peroxisome proliferator, perfluorodecanoic acid and the relationship to phospholipid metabolism in rats.	1999	Toxicology. 1999 Jun 15;134(2-3):179-95. doi: 10.1016/s0300-483x(99)00038-4.	Perfluorodecanoic acid (PFDA) is a potent peroxisome proliferator that causes hepatotoxicity but lacks tumor-promoting activity in rats. We previously showed that a single dose of PFDA at 50 mg/kg (approximately LD50) causes an elevation in liver phosphocholine (PCho) and other effects related to phospholipid metabolism. In this study, we examined metabolic effects in the dose range 2-50 mg/kg in rats. At doses < or =20 mg/kg, PFDA is significantly less hepatotoxic than the LD50 as manifested by electron microscopy and measurements of daily food consumption and body weight. At 50 mg/kg rat serum tumor necrosis factor (TNF)-alpha concentration was increased 8-fold, while at 15 mg/kg there was no apparent increase in this cytokine. This lower dose, however, induces metabolic effects similar to those seen at the LD50. Liver fatty acyl-CoA oxidase activity showed a dose-dependent increase from 5-25 mg/kg PFDA. Treatments at 15 and 50 mg/kg caused a significant increase in liver phosphatidylcholine (28 and 66%) and phosphatidylethanolamine (31 and 74%). Both doses caused a significant increase in liver PCho but did not affect liver ATP levels, as manifested in 31P nuclear magnetic resonance (NMR) spectra from rat livers in vivo. These data suggest that the increase in liver [PCho] observed following PFDA exposure in rats represents a specific metabolic response, rather than a broad-range hepatotoxic effect.			●							-		C	C
1083	実験動物（急性毒性）	Berthiaume, Jessica; Wallace, Kendall B	Perfluorooctanoate, perflourooctanesulfonate, and N-ethyl perfluorooctanesulfonamido ethanol; peroxisome proliferation and mitochondrial biogenesis	2002	Toxicol Lett. 2002 Mar 24;129(1-2):23-32. doi: 10.1016/s0378-4274(01)00466-0.	Compounds that cause peroxisome proliferation in rats and mice have been reported to interfere with mitochondrial (mt) bioenergetics and possibly biogenesis. The purpose of this investigation was to establish whether proliferation of peroxisomes and mitochondria are necessarily related. Perfluorooctanesulfonate (PFOS) and N-ethyl perfluorooctanesulfonamido ethanol (N-EtFOSE) were investigated as peroxisome proliferators in comparison to perfluorooctanoic acid (PFOA). Three parameters were chosen to assess peroxisome proliferation, stimulation of lauroyl CoA oxidase activity, reduction of serum cholesterol concentration, and hepatomegaly. mt Biogenesis was assessed through cytochrome oxidase activity, cytochrome content and mitochondrial DNA (mtDNA) copy number. PFOA, PFOS, or N-EtFOSE was administered via a single i.p. injection at 100 mg/kg in male rats, and measurements were made 3 days later. In this model, PFOS and PFOA share similar potencies as peroxisome proliferators, whereas N-EtFOSE showed no activity. mt Endpoints were altered only in the PFOA treatment group, which consisted of a decrease cytochrome oxidase activity in liver tissue and an increase in the mtDNA copy number. None of the perfluorooctanoates significantly altered mt cytochrome content following acute in vivo treatment. These data demonstrate that acute administration of PFOS or PFOA causes hepatic peroxisome proliferation in rats. However, stimulation of mt biogenesis is not a characteristic response of all peroxisome proliferators.			●							-		B	B
1084	実験動物（急性毒性）	Brewster, D W; Birnbaum, L S	The biochemical toxicity of perfluorodecanoic acid in the mouse is different from that of 2,3,7,8-tetrachlorodibenzo-p-dioxin	1989	Toxicol Appl Pharmacol. 1989 Jul;99(3):544-54. doi: 10.1016/0041-008x(89)90161-0.	Perfluorodecanoic acid (PFDA) is an industrial surfactant that has been reported to produce signs of toxicity in rats similar to those due to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). In order to characterize the biochemical toxicity of PFDA in the mouse and to determine whether PFDA toxicity is mediated by the Ah locus, congenic female C57BL/6J mice differing only at the Ah locus (normal homozygous responsive Ahb/b, heterozygous responsive Ahb/d, and homozygous nonresponsive Ahd/d) were administered a single oral dose of PFDA. The wild type (Ahb/b) mice were killed 2, 7, 14, or 30 days after administration of 0, 40, 80, 100, 120, or 160 mg PFDA/kg. Mice from the other two congenic strains were killed 30 days after dosing with 0, 40, 80, or 160 mg/kg. PFDA produced a 2.5-fold increase in absolute liver weight, a 5- to 15-fold increase in hepatic fatty acyl Co-A oxidase activity, and a 70% decrease in hepatic ethoxyresorufin O-deethylase (EROD) activity. These effects were dose and time dependent. Total hepatic lipids were increased at an early time point and at the lowest dose. At later time periods and/or higher doses, the lipid concentration was decreased approximately 20% from that of controls. Hepatic protein concentrations were depressed approximately 25% from control levels 30 days after treatment. There was little difference in any of these parameters between responsive (Ahb/b, Ahb/d) and nonresponsive (Ahd/d) mice. These results suggest that the Ah allele has little effect in regulating the toxicity of PFDA in the mouse and that the biochemical response to PFDA in the mouse is markedly different from that of TCDD. Furthermore, the biochemical response to PFDA in the mouse is different from that reported in the rat.			●	●						-		B	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	評価書引用 EPA_PFOA_2021	評価書引用 EFSA_2020	評価書引用 ATSDR_2021	評価書引用 Health Canada_PFOS_2018	評価書引用 Health Canada_PFOA_2018	評価書引用 FSANZ_2017	評価書引用 FSANZ_2021 (Immunomodulation)	評価書引用 WHO_2022	備考	情報抽出対象	文献ランク①	文献ランク②
1085	実験動物（急性毒性）	Cheng, Xingguo; Klaassen, Curtis D	Perfluorocarboxylic acids induce cytochrome P450 enzymes in mouse liver through activation of PPAR-alpha and CAR transcription factors	2008	Toxicol Sci. 2008 Nov;106(1):29-36. doi: 10.1093/toxsci/kfn147. Epub 2008 Jul 22.	Cytochrome p450 enzymes (Cyps) are major phase-I xenobiotic-metabolizing enzymes. Cyps are regulated by many environmental chemicals and drugs. However, knowledge about regulation of Cyps by perfluorocarboxylic acids (PFCAs), which are persistent in the environment, is limited. Two days after a single i.p. administration (50 mg/kg) of perfluorooctanoic acid (PFOA) and perfluorodecanoic acid (PFDA) increased mRNA expression of Cyp2B10 (20-fold), 3A11 (two-fold), and 4A14 (32-fold), but not Cyp1A1/2 in mouse livers. PFDA and PFOA also markedly increased protein expression of Cyp2B (50-fold) and 4A (10-fold). PFDA increased Cyp4A14 mRNA expression at relatively low doses (0.5 mg/kg), but increased Cyp2B10 mRNA expression only at high doses (> 20 mg/kg). By using constitutive androstane receptor (CAR)-, pregnane-X receptor (PXR)-, peroxisome proliferator-activated receptor alpha (PPAR)-alpha-, and farnesoid X receptor-null mouse models, PPAR-alpha and CAR were shown to play central roles in the induction of Cyps by PFDA. Specifically, PFDA increased Cyp4A14 mRNA expression in wild-type (WT) mice, but much less in PPAR-alpha-null mice. PFDA increased Cyp2B10 mRNA expression in WT mice, but not in CAR-null mice. In addition, PFDA increased mRNA expression and nuclear translocation of the transcription factor CAR. Therefore, the current studies provide important insight into understanding the regulatory mechanisms initiated by PFCAs, and may help to better predict and understand the toxicokinetics and toxicodynamics of various PFCAs. In conclusion, PFCAs increased Cyp2B10 and 4A14 expression by activating PPAR-alpha and CAR nuclear receptors, respectively. PPAR-alpha is activated at much lower doses of PFDA than CAR.			●	●						-		B	B
1086	実験動物（急性毒性）	Finlay, C.	8-2 Telomer B Alcohol: acute oral toxicity-fixed dose method	2008	DuPont-6711. (as cited in ECHA, 2012, CLH report).	No abstract available			●							企業データ		D	D
1087	実験動物（急性毒性）	Luo, Min; Tan, Zhen; Dai, Manyun; Song, Danjun; Lin, Jiao; Xie, Minzhu; Yang, Julin; Sun, Lu; Wei, Dengming; Zhao, Jinshun; Gonzalez, Frank J; Liu, Aiming	Dual action of peroxisome proliferator-activated receptor alpha in perfluorodecanoic acid-induced hepatotoxicity	2017	Arch Toxicol. 2017 Feb;91(2):897-907. doi: 10.1007/s00204-016-1779-7. Epub 2016 Jun 25.	Perfluorodecanoic acid (PFDA) is widely used in production of many daily necessities based on their surface properties and stability. It was assigned as a Persistent Organic Pollutant in 2009 and became a public concern partly because of its potential for activation of the peroxisome proliferator-activated receptor alpha (PPARα). In this study, wild-type and Ppara-null mice were administered PFDA (80 mg/kg). Blood and liver tissues were collected and subjected to systemic toxicological and mechanistic analysis. UPLC-ESI-QTOFMS-based metabolomics was used to explore the contributing components of the serum metabolome that led to variation between wild-type and Pparα-null mice. Bile acid homeostasis was disrupted, and slight hepatocyte injury in wild-type mice accompanied by adaptive regulation of bile acid synthesis and transport was observed. The serum metabolome in wild-type clustered differently from that in Pparα-null, featured by sharp increases in bile acid components. Differential toxicokinetic tendency was supported by regulation of UDP-glucuronosyltransferases dependent on PPARα, but it did not contribute to the hepatotoxic responses. Increase in Il-10 and activation of the JNK pathway indicated inflammation was induced by disruption of bile acid homeostasis in wild-type mice. Inhibition of p-p65 dependent on PPARα activation by PFDA stopped the inflammatory cascade, as indicated by negative response of Il-6, Tnf-α, and STAT3 signaling. These data suggest disruptive and protective role of PPARα in hepatic responses induced by PFDA.			●							-		C	C
1088	実験動物（急性毒性）	Rockwell, Cheryl E; Turley, Alexandra E; Cheng, Xingguo; Fields, Patrick E; Klaassen, Curtis D	Acute immunotoxic effects of perfluorononanoic acid (PFNA) in C57BL/6 mice	2013	Clin Exp Pharmacol. 2013;Suppl 4:S4-002. doi: 10.4172/2161-1459.S4-002.	otrganic perfluorochemicals (PFCs) have become an environmental concern due to widespread detection in human blood and experimental evidence for immune, developmental, and liver toxicity. Whereas the blood concentrations of many PFCs are declining, blood levels of Perfluorononanoic Acid (PFNA) are rising in the United States. The purpose of the present studies was to determine the effects of PFNA on lymphoid organs and immune cells of C57BL/6 mice. The present study demonstrates that PFNA produces immunotoxic effects in both male and female C57BL/6 mice as evidenced by splenic atrophy, decreased splenocyte numbers, and a marked reduction in thymocyte viability. The current study also demonstrates that the effects of PFNA on different leukocyte populations are not uniform. The CD4(+)CD8(+) double-positive thymocytes were particularly sensitive to PFNA in which the proportion of this population was >95% decreased relative to the entire CD4(+) thymocyte population in PFNA-treated mice. Interestingly, PFNA also markedly increased serum levels of TNFα in response to LPS in mice. Collectively, the present studies demonstrate that PFNA decreases lymphocyte viability and alters the immune response to LPS in C57BL/6 mice.			●	●						-		C	C
1089	実験動物（急性毒性）	Rockwell, Cheryl E; Turley, Alexandra E; Cheng, Xingguo; Fields, Patrick E; Klaassen, Curtis D	Persistent alterations in immune cell populations and function from a single dose of perfluorononanoic acid (PFNA) in C57Bl/6 mice	2017	Food Chem Toxicol. 2017 Feb;100:24-33. doi: 10.1016/j.fct.2016.12.004. Epub 2016 Dec 8.	Perfluorononanoic acid (PFNA) is a perfluoroalkyl substance (PFAS) that is structurally related to perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS). Whereas PFOA and PFOS are known immunotoxicants, PFNA is less well characterized. Our previous study showed that PFNA has immunomodulatory effects on leukocyte populations and immune function. The present studies sought to determine whether, and to what degree, the immune system recovered 28 days after PFNA exposure. None of the parameters measured had fully recovered. A few parameters had partially recovered, including decreased spleen size and the decreased ratio of the CD4(+)/CD8(+) double-positive population in thymus. The majority of effects of PFNA remained unchanged 28 days after exposure, including decreased proportion of intact thymocytes (as determined by FSC vs SSC), alterations in the ratios of immune cell populations in spleen and the CD4(+), CD8(+) and double-negative populations in thymus. Notably, PFNA markedly increased the TNFα response to LPS in vivo, and no recovery was evident 28 days after exposure. The effect of PFNA on CD4(+) T cells, CD8(+) T cells and CD19(+) cells was more pronounced in females. The current study demonstrates that a single high dose exposure to PFNA (e.g. as might occur accidentally in an occupational setting) has long-lasting effects on the immune system.			●	●						-		D	C
1090	実験動物（肝毒性）	Kennedy, G L Jr; Hall, G T; Brittelli, M R; Barnes, J R; Chen, H C	Inhalation toxicity of ammonium perfluorooctanoate	1986	Food Chem Toxicol. 1986 Dec;24(12):1325-9. doi: 10.1016/0278-6915(86)90066-9.	Ammonium perfluorooctanoate (CAS Registry No. 3825-26-1) is a fine white powder which can become airborne; hence its inhalation toxicity was studied in the male rat. The compound was found to be moderately toxic following single 4-hr exposures, with an LC50 of 980 mg/m3. This concentration produced both an increase in liver size and corneal opacity. Both findings diminished with increasing time after exposure. Subchronic head-only inhalation exposures (6 hr/day on 5 days/wk for 2 wk to 0, 1, 8 or 84 mg/m3) suppressed body-weight gain at 84 mg/m3. Reversible liver-weight increases, reversible increases in serum enzyme activities, and microscopic liver pathology, including necrosis, occurred at exposure of 8 and 84 mg/m3. No ocular changes were produced. Concentrations of organofluoride in the blood showed a dose relationship with initial levels of 108 ppm in rats treated at 84 mg/m3 falling to 0.84 ppm after 84 days with a blood half-life of 5-7 days. The no-observed-effect level was 1 mg/m3 and a mean organofluoride blood level of 13 ppm was detected in rats immediately after the tenth exposure to an atmospheric level of 1 mg ammonium perfluorooctanoate/m3.				●		●				-	1	B	A
1091	実験動物（吸入毒性）	Kinney, L A; Chromey, N C; Kennedy, G L Jr	Acute inhalation toxicity of ammonium perfluorononanoate	1989	Food Chem Toxicol. 1989 Jul;27(7):465-8. doi: 10.1016/0278-6915(89)90033-1.	Ammonium perfluorononanoate (CAS Registry No. 4149-60-4) is a white powder that can become airborne. Its acute inhalation toxicity in male rats was studied. Male rats were exposed for single 4-hr periods to dust concentrations ranging from 67 to 4600 mg/m3. The LC50 was determined to be 820 mg/m3, with the lowest concentration causing death being 590 mg/m3. Ammonium perfluorononanoate was classified as moderately toxic by the acute inhalation route. Exposure to ammonium perfluorononanoate caused a pronounced increase in liver size. The acute toxicity of ammonium perfluorononanoate appears to be similar to that of its 8-carbon homologue, ammonium perfluorooctanoate, but considerably less than that of the 10-carbon homologue, perfluoro-n-decanoic acid.				●						-		C	B
1092	実験動物（急性毒性）	Bio/Dynamics, Inc.	An acute inhalation toxicity study of T-2306 CoC in the rat	1979	Bio/Dynamics, Inc. #78-7185. [As cited in Health Canada (2006)].	No abstract available					●		●			企業データ		D	D
1093	実験動物（急性毒性）	Corning Hazleton Inc.	Final report: Primary eye irritation/corrosion study of T-6684 in rabbits (OECD Guidelines)	1997	Corning Hazleton Inc. #61101151. [As cited in Health Canada (2006)].	No abstract available					●					企業データ		D	D
1094	実験動物（急性毒性）	Dean, W.P. and Jessup, D.C.	Acute oral toxicity (LD50) study in rats	1978	U.S. Environmental Protection Agency Administrative Record 226-0419.	No abstract available					●	●				U.S. Environmental Protection Agency Administrative Record 226-0419.で検索したが入手不可		D	D
1095	実験動物（急性毒性）	Hazleton Labs	Primary eye irritation study in rabbits — method, summary, raw data appendix	1987	Hazleton Laboratories America Inc. #70100355, sample T-4016. [As cited in Health Canada (2006)].	No abstract available					●					企業データ		D	D
1096	実験動物（急性毒性）	Hazleton Wisconsin Inc.	Final report: Primary eye irritation/corrosion study of PFOS (T-5898) in rabbits (OECD Guidelines)	1994	Hazleton Wisconsin Inc. #40200470. [As cited in Health Canada (2006)].	No abstract available					●					企業データ		D	D
1097	実験動物（急性毒性）	Riker Laboratories Inc.	Acute ocular irritation test with T-2997CoC in albino rabbits	1981	Riker Laboratories Inc. #0882EB0009. [As cited in Health Canada (2006)].	No abstract available					●					企業データ		D	D

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献ランク①	文献ランク②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1098	実験動物（急性毒性）	Rusch, G.	An acute inhalation study of T-2305 CoC in the rat	1979	U.S. Environmental Protection Agency Administrative Record 226-0417.	No abstract available					●	●				U.S. Environmental Protection Agency Administrative Record 226-0417.で検索したが入手不可		D	D
1099	実験動物（急性毒性）	Gabriel, K.	Acute oral toxicity—rats	1976	U.S. Environmental Protection Agency Administrative Record 226-0425.	No abstract available						●				U.S. Environmental Protection Agency Administrative Record 226-0425. で検索したが入手不可		D	D
1100	実験動物（急性毒性）	Glaza, S.	Acute dermal toxicity study of T-6342 in rabbits	1995	U.S. Environmental Protection Agency Administrative Record 226–0427.	No abstract available						●				U.S. Environmental Protection Agency Administrative Record 226-0427. で検索したが入手不可		D	D
1101	実験動物（急性毒性）	Glaza, S.M.	Acute oral toxicity study of T-6669 in rats	1997	U.S. Environmental Protection Agency Administrative Record 226-0420.	No abstract available						●				U.S. Environmental Protection Agency Administrative Record 226-0420. で検索したが入手不可		D	D
1102	実験動物（肝毒性）	Butenhoff, J.; Costa, G.; Elcombe, C.; Farrar, D.; Hansen, K.; Iwai, H.; Jung, R.; Kennedy, G.; Lieder, P.; Olsen, G.; Thomford, P.	Toxicity of ammonium perfluorooctanoate in male cynomolgus monkeys after oral dosing for 6 months	2002	Toxicol Sci. 2002 Sep;69(1):244-57. doi: 10.1093/toxsci/69.1.244.	Ammonium perfluorooctanoate (APFO) is a processing aid in the production of fluoropolymers that has been shown to have a long half-life in human blood. To understand the potential toxicological response of primates, groups of male cynomolgus monkeys were given daily po (capsule) doses of either 0, 3, 10, or 30 (reduced to 20) mg/kg/day for 26 weeks. Two monkeys from each of the control and 10 mg/kg/day dose groups were observed for 90 days after the last dose. Clinical observations, clinical chemistry, determination of key hormones, gross and microscopic pathology, cell proliferation, peroxisomal proliferation, bile-acid determination, and serum and liver perfluorooctanoate (PFOA) concentrations were monitored. Toxicity, including weight loss and reduced food consumption, was noted early in the study at the 30 mg/kg/day dose; therefore, the dose was reduced to 20 mg/kg/day. The same signs of toxicity developed in 3 monkeys at 20 mg/kg/day, after which treatment of these monkeys was discontinued. One 30/20 mg/kg/day monkey developed the signs of toxicity noted above and a possible dosing injury, and this monkey was sacrificed in extremis on Day 29 A 3 mg/kg/day dose-group monkey was sacrificed in extremis on Day 137 for reasons not clearly related to APFO treatment. Dose-dependent increases in liver weight as a result of mitochondrial proliferation occurred in all APFO-treated groups. Histopathologic evidence of liver injury was not observed at either 3 or 10 mg/kg/day. Evidence of liver damage was seen in the monkey sacrificed in moribund condition at the highest dose. Body weights were decreased at 30/20 mg/kg. PFOA concentrations in serum and liver were highly variable, were not linearly proportional to dose, and cleared to background levels within 90 days after the last dose. A no observable effect level was not established in this study, and the low dose of 3 mg/kg/day was considered the lowest observable effect level based on increased liver weight and uncertainty as to the etiology leading to the moribund sacrifice of one low-dose monkey on Day 137 Other than those noted above, there were no APFO-related macroscopic or microscopic changes, changes in clinical chemistry, hormones, or urinalysis, or hematological effects. In particular, effects that have been associated with the development of pancreatic and testicular toxicity in rats were not observed in this study.	●	●		●		●	●		●	-	1	A	A
1103	実験動物（反復投与毒性）	Chang, S.; Allen, B. C.; Andres, K. L.; Ehresman, D. J.; Falvo, R.; Provencher, A.; Olsen, G. W.; Butenhoff, J. L.	Evaluation of serum lipid, thyroid, and hepatic clinical chemistries in association with serum perfluorooctanesulfonate (PFOS) in cynomolgus monkeys after oral dosing with potassium PFOS	2017	Toxicol Sci. 2017 Apr 1;156(2):387-401. doi: 10.1093/toxsci/kfw267.	An oral dose study with perfluorooctanesulfonate (PFOS) was undertaken to identify potential associations between serum PFOS and changes in serum clinical chemistry parameters in purpose-bred young adult cynomolgus monkeys (Macaca fascicularis). In this study, control group (n = 6/sex) was sham-dosed with vehicle (0.5% Tween 20 and 0.05 ethanol in water), low-dose group (n = 6/sex) received 1 single K+PFOS dose (9 mg/kg), and high-dose group (n = 4-6/sex) received 3 separate K+ PFOS doses (11-17.2 mg/kg). Monkeys were given routine checkups and observed carefully for health problems on a daily basis. Scheduled blood samples were drawn from all monkeys prior to, during, and after K+PFOS administration for up to 1 year and they were analyzed for PFOS concentrations and clinical chemistry markers for coagulation, lipids, hepatic, renal, electrolytes, and thyroid-related hormones. No mortality occurred during the study. All the monkeys were healthy, gained weight, and were released back to the colony at the end of the study. The highest serum PFOS achieved was approximately 165 µg/ml. When compared with time-matched controls, administration of K+PFOS to monkeys did not result in any toxicologically meaningful or clinically relevant changes in serum clinical measurements for coagulation, lipids, hepatic, renal, electrolytes, and thyroid-related hormones. A slight reduction in serum cholesterol (primarily the high-density lipoprotein fraction), although not toxicologically significant, was observed. The corresponding lower-bound fifth percentile benchmark concentrations (BMCL1sd) were 74 and 76 µg/ml for male and female monkeys, respectively. Compared to the 2013-2014 geometric mean serum PFOS level of 4.99 ng/ml (0.00499 µg/ml) in US general population reported by CDC NHANES, this represents 4 orders of magnitude for margin of exposure.	●	●	●	●						-		B	B
1104	実験動物（免疫毒性）	Cui, L.; Zhou, Q. F.; Liao, C. Y.; Fu, J. J.; Jiang, G. B.	Studies on the toxicological effects of PFOA and PFOS on rats using histological observation and chemical analysis	2009	Arch Environ Contam Toxicol. 2009 Feb;56(2):338-49. doi: 10.1007/s00244-008-9194-6. Epub 2008 Jul 26.	As an emerging class of environmentally persistent and bioaccumulative contaminants, perfluorinated compounds (PFCs), especially perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), have been ubiquitously found in the environment. Increasing evidence shows that the accumulated levels of PFCs in animals and the human body might cause potential impairment to their health. In the present study, toxicological effects of PFOA and PFOS on male Sprague-Dawley rats were examined after 28 days of subchronic exposure. Abnormal behavior and sharp weight loss were observed in the high-dose PFOS group. Marked hepatomegaly, renal hypertrophy, and orchioncus in treated groups were in accordance with the viscera-somatic indexes of the liver, kidney, and gonad. Histopathological observation showed that relatively serious damage occurred in the liver and lung, mainly including hepatocytic hypertrophy and cytoplasmic vacuolation in the livers and congestion and thickened epithelial walls in the lungs. PFOA concentrations in main target organs were in the order of kidney > liver > lung > (heart, whole blood) > testicle > (spleen, brain), whereas the bioaccumulation order for PFOS was liver > heart > kidney > (whole blood) > lung > (testicle, spleen, brain). The highest concentration of PFOA detected in the kidney exposed to 5 mg/kg/day was 228+/-37microg/g and PFOS in the liver exposed to 20 mg/kg/day reached the highest level of 648+/-17 microg/g, indicating that the liver, lung, and kidney might serve as the main target organs for PFCs. Furthermore, a dose-dependent accumulation of PFOS in various tissues was found. The accumulation levels of PFOS were universally higher than PFOA, which might explain the relative high toxicity of PFOS. The definite toxicity and high accumulation of the tested PFCs might pose a great threat to biota and human beings due to their widespread application in various fields.	●	●		●	●	●	●		●	-	1	B	A

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報抽出対象	文献ランク①	文献ランク②
1105	実験動物（反復投与毒性）	Han, R.; Zhang, F.; Wan, C.; Liu, L.; Zhong, Q.; Ding, W.	Perfluorooctane sulphonate induces oxidative hepatic damage via mitochondria-dependent and NF-κB/TNF-α-mediated pathway	2018	Chemosphere 191: 1056-1064. doi: 10.1016/j.chemosphere.2017.08.070	Perfluorooctane sulfonate (PFOS), one member of polyfluoroalkyl chemicals (PFASs), persist in the environment and are found in relatively high concentrations in animal livers. PFOS has been shown to induce tumour of the liver in rats following chronic dietary administration. However, the molecular mechanisms involved in PFOS-induced hepatocellular hypertrophy are still not well characterized. In this study, male Sprague-Dawley rats were daily gavaged with PFOS (1 or 10 mg/kg body weight) for 28 days. Rat primary cultured Kupffer cells or hepatocytes were exposed to 100 μM PFOS for 0-48 h. Our results showed that PFOS exposure caused serious hepatocellular damage and obvious inflammatory cell infiltration and increased serum tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6) levels. Particularly, PFOS exposure triggered Kupffer cell activation and significantly upregulated the expression of proliferating cell nuclear antigen (PCNA), c-Jun, c-MYC and Cyclin D1 (CyD1) in liver. In vitro, PFOS significantly induced production of TNF-α and IL-6 in Kupffer cells and increased PCNA, c-Jun, c-MYC and CyD1 expression in the primary hepatocytes co-cultured with Kupffer cells. However, Kupffer cell activation was mostly abolished by anti-TNF-α or anti-IL6 treatment. Furthermore, blockage of TNF-α and IL-6 significantly inhibited hepatocyte proliferation by gadolinium chloride (GdCl3) pre-treatment in PFOS-treated mice and primary cultured Kupffer cells. On the other hand, NF-κB inhibitor (PDTC) and c-Jun amino-terminal kinase (JNK) inhibitor (SP600125) significantly inhibited production of PFOS-induced TNF-α and IL-6. Taken together, these data suggest that PFOS induces Kupffer cell activation, leading to hepatocyte proliferation by through the NF-κB/TNF-α/IL-6-dependent pathway.	●	●	●							-		B	B
1106	実験動物（反復投与毒性）	Lai, K. P.; Ng, A. H.; Wan, H. T.; Wong, A. Y.; Leung, C. C.; Li, R.; Wong, C. K.	Dietary exposure to the environmental chemical, pfos on the diversity of gut microbiota, associated with the development of metabolic syndrome	2018	Front Microbiol. 2018 Oct 24;9:2552. doi: 10.3389/fmicb.2018.02552. eCollection 2018.	The gut microbiome is a dynamic ecosystem formed by thousands of diverse bacterial species. This bacterial diversity is acquired early in life and shaped over time by a combination of multiple factors, including dietary exposure to distinct nutrients and xenobiotics. Alterations of the gut microbiota composition and associated metabolic activities in the gut are linked to various immune and metabolic diseases. The microbiota could potentially interact with xenobiotics in the gut environment as a result of their board enzymatic capacities and thereby affect the bioavailability and toxicity of the xenobiotics in enterohepatic circulation. Consequently, microbiome-xenobiotic interactions might affect host health. Here, we aimed to investigate the effects of dietary perfluorooctane sulfonic acid (PFOS) exposure on gut microbiota in adult mice and examine the induced changes in animal metabolic functions. In mice exposed to dietary PFOS for 7 weeks, body PFOS and lipid contents were measured, and to elucidate the effects of PFOS exposure, the metabolic functions of the animals were assessed using oral glucose-tolerance test and intraperitoneal insulin-tolerance and pyruvate-tolerance tests; moreover, on Day 50, cecal bacterial DNA was isolated and subject to 16S rDNA sequencing. Our results demonstrated that PFOS exposure caused metabolic disturbances in the animals, particularly in lipid and glucose metabolism, but did not substantially affect the diversity of gut bacterial species. However, marked modulations were detected in the abundance of metabolism-associated bacteria belonging to the phyla Firmicutes, Bacteroidetes, Proteobacteria, and Cyanobacteria, including, at different taxonomic levels, Turicibacteraceae, Turicibacterales, Turicibacter, Dehalobacteriaceae, Dehalobacterium, Allobaculum, Bacteroides acidifaciens, Alphaproteobacteria, and 4Cod-2/YS2. The results of PICRUSt analysis further indicated that PFOS exposure perturbed gut metabolism, inducing notable changes in the metabolism of amino acids (arginine, proline, lysine), methane, and a short-chain fatty acid (butanoate), all of which are metabolites widely recognized to be associated with inflammation and metabolic functions. Collectively, our study findings provide key information regarding the biological relevance of microbiome-xenobiotic interactions associated with the ecology of gut microbiota and animal energy metabolism.	●	●	●							-		B	B
1107	実験動物（反復投与毒性）	NTP	NTP technical report on the toxicity studies of perfluoroalkyl sulfonates (perfluorobutane sulfonic acid, perfluorohexane sulfonate potassium salt, and perfluorooctane sulfonic acid) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats	2019	NTP (Toxicity Report 96). Research Triangle Park, NC.	No abstract available	●									NTP TR	1	D	D
1108	実験動物（肝毒性）	Perkins, Roger G; Butenhoff, John L; Kennedy, Gerald L Jr; Palazzolo, Matthew J	13-week dietary toxicity study of ammonium perfluorooctanoate (APFO) in male rats	2004	Drug Chem Toxicol. 2004 Nov;27(4):361-78. doi: 10.1081/dct-200039773.	Ammonium perfluorooctanoate is a perfluorinated carboxylate that is used commercially as a processing aid in the production of fluorinated polymers. Perfluorooctanoate (PFOA) has been found in human blood of the general population from exogenous sources. This report presents the results of a 13-week dietary toxicity study in male rats and was designed to identify potential target organ(s), dose response, and to explore possible relationships of PPARalpha activation to potential liver effects and hormonal changes. Rats were fed dietary levels of 0, 1, 10, 30, and 100 ppm (equivalent to 0, 0.06, 0.64, 1.94, and 6.5 mg/kg/day) for 13 weeks. A control group pair-fed adjusted to the 100 ppm level and groups allowed to recover for 8 weeks were included. Sacrifices were conducted after 4, 7, and 13 weeks of feeding and after 8 weeks of recovery. At each sacrifice, gross and histopathology was conducted on selected tissues and measurements of hepatic palmitoyl CoA oxidase (PCoAO), as well as serum estradiol, luteinizing hormone, testosterone, and PFOA were determined. There were no clinical signs or mortality. Body weight gains were reduced in the 100 ppm dose group. Liver weights (absolute and relative), PCoAO activity, and hepatocyte hypertrophy (minimal to mild) were increased in the 10 ppm dose group and above and were reversible in recovery. Under the study conditions, hormone levels appeared unchanged. PFOA serum concentrations increased in a dose-related fashion, appeared to reach steady-state by test week 5, and declined rapidly through the recovery period. Serum PFOA concentrations at the end of the treatment period were 7.1, 41, 70, and 138 microg/mL in the 1, 10, 30 and 100 ppm dose groups. The study no effect level was 1 ppm (0.06 microg/mg) with doses of 10 ppm (0.64 microg/mg) and higher producing adaptive and reversible liver changes.	●	●		●	●	●	●		●	-	1	A	A
1109	実験動物（反復投与毒性）	Seacat, A. M.; Thomford, P. J.; Hansen, K. J.; Clemen, L. A.; Eldridge, S. R.; Elcombe, C. R.; Butenhoff, J. L.	Sub-chronic dietary toxicity of potassium perfluorooctanesulfonate in rats [Erratum]	2003	Toxicology. 2003 Feb 1;183(1-3):117-31. doi: 10.1016/s0300-483x(02)00511-5.	Perfluorooctanesulfonate (PFOS) is a widely disseminated persistent compound found at low (part-per-billion) concentrations in serum and liver samples from humans and fish-eating wildlife. This study investigated the hypotheses that early hepatocellular peroxisomal proliferation and hepatic cellular proliferation are factors in chronic liver response to dietary dosing, that lowering of serum total cholesterol is an early clinical measure of response to treatment, and that liver and serum PFOS concentrations are proportional to dose and cumulative dose after sub-chronic treatment. PFOS was administered in diet as the potassium salt at 0, 0.5, 2.0, 5.0, and 20 parts per million (ppm) to Sprague Dawley rats for 4 or 14 weeks. At 4 weeks, effects included decreased serum glucose and an equivocal (<twofold) increase in hepatic palmitoyl CoA oxidase (PCoAO) activity in 20 ppm dose-group males in one of two assay systems [corrected]. At 14 weeks, the 20 ppm males had increased liver weight, decreased serum cholesterol, increased non-segmented neutrophils, and increased ALT. Relative liver weights and urea nitrogen were increased in both sexes at 14 weeks. Hepatocytic hypertrophy and cytoplasmic vacuolation were observed in the 5 or 20 ppm male and the 20 ppm female dose groups. An increase in hepatic PCoAO activity was not observed at 14 weeks, and the average hepatocyte proliferation index was not increased, although, individual animals had mild increases. Serum and liver PFOS concentrations were proportional to dose and cumulative dose. Serum concentrations were generally higher in females than in males. The liver-to-serum PFOS ratios ranged from approximately 3:1 to 12:1. After 14 weeks, the no-observed-adverse effect level (NOAEL) in males and females was 5 ppm. The NOAEL corresponded to mean serum PFOS concentrations of 44 ppm (microg/ml) in males and 64 ppm in females and mean liver PFOS concentrations of 358 ppm in males and 370 ppm in females. Results for this study: (1) did not provide strong evidence for hepatocellular peroxisomal or cellular proliferation at the doses tested; (2) suggested that lowering of serum total cholesterol may not be the earliest clinically-measurable response to treatment in the rat; and (3) confirmed that serum and liver PFOS concentrations on repeated dosing are proportional to dose and cumulative dose.	●	●		●	●		●		●	-		B	B
1110	実験動物（反復投与毒性）→実験動物（肝毒性）	Seacat, A. M.; Thomford, P. J.; Hansen, K. J.; Olsen, G. W.; Case, M. T.; Butenhoff, J. L.	Subchronic toxicity studies on perfluorooctanesulfonate potassium salt in cynomolgus monkeys	2002	Toxicol Sci. 2002 Jul;68(1):249-64. doi: 10.1093/toxsci/68.1.249.	This study was conducted to determine the earliest measurable response of primates to low-level perfluorooctanesulfonate (PFOS) exposure and to provide information to reduce uncertainty in human health risk assessment. Groups of male and female monkeys received 0, 0.03, 0.15, or 0.75 mg/kg/day potassium PFOS orally for 182 days. Recovery animals from each group, except the 0.03 mg/kg/day dose group, were monitored for one year after treatment. Significant adverse effects occurred only in the 0.75 mg/kg/day dose group and included compound-related mortality in 2 of 6 male monkeys, decreased body weights, increased liver weights, lowered serum total cholesterol, lowered triiodothyronine concentrations (without evidence of hypothyroidism), and lowered estradiol levels. Decreased serum total cholesterol occurred in the 0.75 mg/kg/day dose group at serum PFOS levels > 100 ppm. Hepatocellular hypertrophy and lipid vacuolation were present at term in the 0.75 mg/kg/day dose group. No peroxisomal (palmitoyl CoA oxidase) or cell proliferation (proliferating cell nuclear antigen immunohistochemistry) was detected. Complete reversal of clinical and hepatic effects and significant decreases in serum and liver PFOS occurred within 211 days posttreatment. Liver-to-serum PFOS ratios were comparable in all dose groups, with a range of 1:1 to 2:1. Serum concentrations associated with no adverse effects (0.15 mg/kg/day) were 82.6 +/- 25.2 ppm for males and 66.8 +/- 10.8 ppm for females. Comparison of serum PFOS concentrations associated with no adverse effect in this study to those reported in human blood samples (0.028 +/- 0.014 ppm) indicated an adequate margin of safety.	●	●		●	●		●		●	-	1	A	A

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献クラン①　B	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1111	実験動物（反復投与毒性）	Xing, J.; Wang, G.; Zhao, J.; Wang, E.; Yin, B.; Fang, D.; Zhao, J.; Zhang, H.; Chen, Y. Q.; Chen, W.	Toxicity assessment of perfluorooctane sulfonate using acute and subchronic male C57BL/6J mouse models	2016	Environ Pollut. 2016 Mar;210:388-96. doi: 10.1016/j.envpol.2015.12.008. Epub 2016 Jan 22.	Perfluorooctane sulfonate (PFOS) is a principal representative and the final degradation product of several commercially produced perfluorinated compounds. However, PFOS has a high bioaccumulation potential and therefore can exert toxicity on aquatic organisms, animals, and cells. Considering the widespread concern this phenomenon has attracted, we examined the acute and subchronic toxic effects of varying doses of PFOS on adult male C57BL/6 mice. The acute oral LD50 value of PFOS in male C57BL/6J mice was 0.579 g/kg body weight (BW). Exposure to the subchronic oral toxicity of PFOS at 2.5, 5, and 10 mg PFOS/kg BW/day for 30 days disrupted the homeostasis of antioxidative systems, induced hepatocellular apoptosis (as revealed by the terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling assay), triggered liver injury (as evidenced by the increased serum levels of aspartate aminotransferase, alanine amino transferase, alkaline phosphatase, and gamma-glutamyl transpeptidase and by the altered histology), and ultimately increased the liver size and relative weight of the mice. PFOS treatment caused liver damage but only slightly affected the kidneys and spleen of the mice. This study provided insights into the toxicological effects of PFOS.	●	●		●					●	-		B	B
1112	実験動物（反復投与毒性）	Zheng, Fei; Sheng, Nan; Zhang, Hongxia; Yan, Shengmin; Zhang, Jianhai; Wang, Jianshe	Perfluorooctanoic acid exposure disturbs glucose metabolism in mouse liver	2017	Toxicol Appl Pharmacol. 2017 Nov 15;335:41-48. doi: 10.1016/j.taap.2017.09.019. Epub 2017 Sep 23.	Environmental pollutants such as perfluorooctanoic acid (PFOA) can influence human metabolism processes and are associated with certain metabolic diseases. To investigate the effect of PFOA on liver glucose homeostasis, adult male Balb/c mice were orally administered 1.25mg/kg of PFOA for 28d consecutively. Compared with the control mice, the body weights of the PFOA-treated mice were unchanged following exposure. However, PFOA exposure increased fasting blood glucose levels and decreased glycogen and glucose content in the liver of treated mice, but did not influence blood insulin significantly. The increased blood glucagon might contribute to the hyperglycemia observed in the PFOA-treated group compared with the control group. In addition, pyruvate tolerance tests supported enhanced glucose production ability in PFOA-exposed mice. Consistent with the increase in blood glucose and decrease in hepatic glucose and glycogen, PFOA exposure decreased the protein level of glycogen synthase in the mouse liver, but increased the level of glucokinase. Furthermore, liver pyruvate, as well as mRNA levels of enzymes involved in the Krebs cycle, such as citrate synthase, isocitrate dehydrogenase, and alpha-ketoglutarate dehydrogenase, increased in the PFOA-treated group. PFOA exposure did not affect muscle glucose or glycogen levels. Indirect calorimetry showed higher VO(2) consumption and respiratory quotient values in the PFOA-treated group compared with the control group, implying that PFOA treatment might promote energy consumption in mice, with a reliance on carbohydrates as a primary source of energy. Thus, our findings indicate that subacute exposure to PFOA might enhance glycogenolysis and gluconeogenesis and promote carbohydrate consumption.	●	●	●							-		B	B
1113	実験動物（反復投与毒性）	Abe, Taiki; Takahashi, Mirei; Kano, Makoto; Amaike, Yuto; Ishii, Chizuru; Maeda, Kazuhiro; Kudoh, Yuki; Morishita, Toru; Hosaka, Takuomi; Sasaki, Takamitsu; Kodama, Susumu; Matsuzawa, Atsushi; Kojima, Hiroyuki; Yoshinari, Kouichi	Activation of nuclear receptor CAR by an environmental pollutant perfluorooctanoic acid.	2017	Arch Toxicol. 2017 Jun;91(6):2365-2374. doi: 10.1007/s00204-016-1888-3. Epub 2016 Nov 10.	Perfluorocarboxylic acids (PFCAs) including perfluorooctanoic acid (PFOA) are environmental pollutants showing high accumulation, thermochemical stability and hepatocarcinogenicity. Peroxisome proliferator-activated receptor α is suggested to mediate their toxicities, but the precise mechanism remains unclear. Previous reports also imply a possible role of constitutive androstane receptor (CAR), a key transcription factor for the xenobiotic-induced expression of various genes involved in drug metabolism and disposition as well as hepatocarcinogenesis. Therefore, we have investigated whether PFCAs activate CAR. In wild-type but not Car-null mice, mRNA levels of Cyp2b10, a CAR target gene, were increased by PFOA treatment. PFCA treatment induced the nuclear translocation of CAR in mouse livers. Since CAR activators are divided into two types, ligand-type activators and phenobarbital-like indirect activators, we investigated whether PFCAs are CAR ligands or not using the cell-based reporter gene assay that can detect CAR ligands but not indirect activators. As results, neither PFCAs nor phenobarbital increased reporter activities. Interestingly, in mouse hepatocytes, pretreatment with the protein phosphatase inhibitor okadaic acid prevented an increase in Cyp2b10 mRNA levels induced by phenobarbital as reported, but not that by PFOA. Finally, in human hepatocyte-like HepaRG cells, PFOA treatment increased mRNA levels of CYP2B6, a CAR target gene, as did phenobarbital. Taken together, our present results suggest that PFCAs including PFOA are indirect activators of mouse and human CAR and that the mechanism might be different from that for phenobarbital. The results imply a role of CAR in the hepatotoxicity of PFCAs.			●							-		B	C
1114	実験動物（反復投与毒性）	Chengelis, Christopher P; Kirkpatrick, Jeannie B; Radovsky, Ann; Shinohara, Motoki	A 90-day repeated dose oral (gavage) toxicity study of perfluorohexanoic acid (PFHxA) in rats (with functional observational battery and motor activity determinations)	2009	Reprod Toxicol. 2009 Jun;27(3-4):342-351. doi: 10.1016/j.reprotox.2009.01.006. Epub 2009 Jan 21.	Possible toxic effects of perfluorohexanoic acid (PFHxA) were evaluated when administered orally by gavage to rats at levels up to 200mg/kg/day for 90 days. Lower body weight gains were noted in the 10, 50 and 200mg/kg/day group males (not dose-responsive) throughout dosing. Other changes included lower red blood cell parameters, higher reticulocyte counts and lower globulin in the 200mg/kg/day group males and females, higher liver enzymes in males at 50 and 200mg/kg/day, lower total protein and higher albumin/globulin ratio, and lower cholesterol, calcium in males at 200mg/kg/day. Minimal centrilobular hepatocellular hypertrophy was present in 200mg/kg/day group males and correlated with higher liver weights and slightly higher peroxisome beta oxidation activity at the end of the dosing period. Based on liver histopathology and liver weight changes, the no-observed-adverse-effect level (NOAEL) for oral administration was 50mg/kg/day for males and 200mg/kg/day for females.			●	●						-		B	D
1115	実験動物（反復投与毒性）	Das, Kaberi P; Wood, Carmen R; Lin, Mimi T; Starkov, Anatoly A; Lau, Christopher; Wallace, Kendall B; Corton, J Christopher; Abbott, Barbara D	Perfluoroalkyl acids induced liver steatosis: effects on genes controlling lipid homeostasis	2017	Toxicology. 2017 Mar 1;378:37-52. doi: 10.1016/j.tox.2016.12.007. Epub 2016 Dec 31.	Persistent presence of perfluoroalkyl acids (PFAAs) in the environment is due to their extensive use in industrial and consumer products, and their slow decay. Biochemical tests in rodent demonstrated that these chemicals are potent modifiers of lipid metabolism and cause hepatocellular steatosis. However, the molecular mechanism of PFAAs interference with lipid metabolism remains to be elucidated. Currently, two major hypotheses are that PFAAs interfere with mitochondrial beta-oxidation of fatty acids and/or they affect the transcriptional activity of peroxisome proliferator-activated receptor α (PPARα) in liver. To determine the ability of structurally-diverse PFAAs to cause steatosis, as well as to understand the underlying molecular mechanisms, wild-type (WT) and PPARα-null mice were treated with perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), or perfluorohexane sulfonate (PFHxS), by oral gavage for 7days, and their effects were compared to that of PPARα agonist WY-14643 (WY), which does not cause steatosis. Increases in liver weight and cell size, and decreases in DNA content per mg of liver, were observed for all compounds in WT mice, and were also seen in PPARα-null mice for PFOA, PFNA, and PFHxS, but not for WY. In Oil Red O stained sections, WT liver showed increased lipid accumulation in all treatment groups, whereas in PPARα-null livers, accumulation was observed after PFNA and PFHxS treatment, adding to the burden of steatosis observed in control (untreated) PPARα-null mice. Liver triglyceride (TG) levels were elevated in WT mice by all PFAAs and in PPARα-null mice only by PFNA. In vitro β-oxidation of palmitoyl carnitine by isolated rat liver mitochondria was not inhibited by any of the 7 PFAAs tested. Likewise, neither PFOA nor PFOS inhibited palmitate oxidation by HepG2/C3A human liver cell cultures. Microarray analysis of livers from PFAAs-treated mice indicated that the PFAAs induce the expression of the lipid catabolism genes, as well as those involved in fatty acid and triglyceride synthesis, in WT mice and, to a lesser extent, in PPARα-null mice. These results indicate that most of the PFAAs increase liver TG load and promote steatosis in mice We hypothesize that PFAAs increase steatosis because the balance of fatty acid accumulation/synthesis and oxidation is disrupted to favor accumulation.			●	●						-		B	B
1116	実験動物（反復投与毒性）	Ding, Lina; Hao, Fuhua; Shi, Zhimin; Wang, Yulan; Zhang, Hongxia; Tang, Huiru; Dai, Jiayin	Systems biological responses to chronic perfluorododecanoic acid exposure by integrated metabonomic and transcriptomic studies	2009	J Proteome Res. 2009 Jun;8(6):2882-91. doi: 10.1021/pr9000256.	Perfluorocarboxylic acids (PFCAs) have been widely used in consumer and industrial products, such as food packaging, and found in the blood of both humans and wildlife. Although studies showed a high tendency toward biological accumulation and a variety of toxic effects for PFCAs, the mechanistic aspects of their toxicity remain unknown. In present study, we investigated the dosage-dependent metabonomic and transcriptomic responses of male rats to the exposure to perfluorododecanoic acid (PFDoA) over 110 days. Our NMR-based metabonomics results for both liver tissues and serum demonstrated that PFDoA exposure led to hepatic lipidosis, which was characterized by a severe elevation in hepatic triglycerides and a decline in serum lipoprotein levels. The results from transcriptomic changes induced by PFDoA corroborated these results with changes in gene transcript levels associated with fatty acid homeostasis. These results demonstrate that PFDoA induces hepatic steatosis via perturbations to fatty acid uptake, lipogenesis, and fatty acid oxidation. Several serum metabolites exhibited dose-dependences, providing thorough descriptions of changes induced by PFDoA exposure. These observations yielded novel insights regarding the toxicological mechanism of PFCAs at the systems level.			●							-		C	C
1117	実験動物（反復投与毒性）	Eke, Dilek; Çelik, Ayla; Yilmaz, Mehmet Bertan; Aras, Nurcan; Kocatürk Sel, Sabriye; Alptekin, Davut	Apoptotic gene expression profiles and DNA damage levels in rat liver treated with perfluorooctane sulfonate and protective role of curcumin	2017	Int J Biol Macromol. 2017 Nov;104(Pt A):515-520. doi: 10.1016/j.ijbiomac.2017.06.075. Epub 2017 Jun 17.	Perfluorinated compounds (PFC(s)) such as PFOS and PFOA, are xenobiotics that can be detected worldwide in the environment and humans. PFOS (C(8)F(17)SO(3)(-)) is a fluorinated organic compound has been used for decades in industrial and commercial products. We investigated the genotoxic and apoptotic impact of PFOS in rat liver using comet assay, micronucleus test and apoptotic gene expression methods for caspase 3, caspase 8 and the protective role of curcumin on the PFOS- induced damage under chronic exposure. In this study, rats were treated either with three different PFOS doses only (0.6, 1.25 and 2.5mg/kg) or one dose of curcumin (80mg/kg) or three different doses of PFOS combined with 80mg/kg dose of curcumin by gavage for 30days at 48h intervals. We evaluated the DNA damage via comet assay and micronucleus test. Doses of PFOS increased micronucleus frequency ($p<0.05$) and strongly induced DNA damage in liver in two different parameters; i: the damaged cell percentage and ii: genetic damage index. Curcumin prevented the formation of DNA damage induced by PFOS and curcumin substance applied with PFOS caused a decrease in the micronucleus frequency. PFOS increased apoptotic gene expression but curcumin decreased the expression levels of caspase 3 and 8.			●							-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献ラン①	文献ラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1118	実験動物（反復投与毒性）	Fang, Xuemei; Gao, Guizhen; Xue, Hongyu; Zhang, Xingtao; Wang, Haichao	Exposure of perfluorononanoic acid suppresses the hepatic insulin signal pathway and increases serum glucose in rats	2012	Toxicology. 2012 Apr 11;294(2-3):109-15. doi: 10.1016/j.tox.2012.02.008. Epub 2012 Mar 1.	Exposure to perfluorononanoic acid (PFNA), an increasingly persistent organic pollutant that has been detected in abiotic and biotic matrices, has been demonstrated to cause hepatotoxicity in animals. However, the effects of PFNA on hepatic glucose metabolism have not been fully characterized. In this study, male rats were exposed to 0, 0.2, 1 or 5mg/kg/d PFNA for 14 days to explore the specific effect of PFNA on hepatic glycometabolism and its underlying mechanisms. The results showed that administration of 5mg/kg/d PFNA significantly increased serum glucose and hepatic glycogen in rats. Quantitative real-time PCR analysis showed that PFNA exposure changed the expression levels of several genes related to hepatic glucose metabolism, such as the glucose-6-phosphatase (G6PC) gene and the glucose transporter 2 (GLUT2) gene, which were upregulated, and the glucokinase (GCK) gene and the phosphoinositide-3-kinase, catalytic, alpha polypeptide (PI3Kca) gene, which were decreased. The protein expression levels of phospho-insulin receptor 1(IRS1), phospho-PI3K, phospho-AKT and phospho-phosphoinositide-dependent kinase 1 (PDK1) were decreased in the livers of rats that received 5mg/kg/d PFNA. The expression of phospho-glycogen synthase kinase-3 beta (GSK3β, Ser 9) was increased, which explains the augment of hepatic glycogen. Significant increases in hydrogen peroxide (H(2)O(2)) and malondialdehyde (MDA) were found in the livers of 5mg/kg/d PFNA-treated rats. Thus, exposure to PFNA disordered glucose metabolism via inhibiting hepatic insulin signal pathway, accelerating the output of glucose and increasing glycogen synthesis in the rat liver. Furthermore, the oxidative stress induced by PFNA may be involved in this process.			●	●						-		C	C
1119	実験動物（反復投与毒性）	Fang, Xuemei; Gao, Guizhen; Zhang, Xingtao; Wang, Haichao	Perfluorononanoic acid disturbed the metabolism of lipid in the liver of streptozotocin-induced diabetic rats	2015	Toxicol Mech Methods. 2015;25(8):622-7. doi: 10.3109/15376516.2015.1053649. Epub 2015 Jun 9.	Most studies on the liver toxicity of perfluorinated compounds (PFCs) are focused on healthy individuals, whereas the effects of PFCs on individuals with diabetes mellitus have not been fully characterized. This study aimed to investigate the acute exposure of perfluorononanoic acid (PFNA) on the metabolism of lipid in the liver of streptozotocin-induced diabetic rats. Male diabetic rats were orally dosed by gavage for 7 days with 0, 0.2, 1 and 5 mg/kg/day PFNA. The contents of lipid, the activities of enzyme, the expressions of protein in the liver and the serum parameters were detected. The results indicate that dose-dependent accumulation of triglyceride and total cholesterol occurred in the livers of diabetic rats after PFNA treatment. PFNA increased the activities of lipid synthetase, fatty acid synthease, glucose-6-phosphate dehydrogenase and decreased the activity of lipolytic enzyme, hepatic lipase, in the liver of diabetic rats. The changes of the isocitrate dehydrogenase, malicenzyme and lipoprotein lipase were not obvious. The expressions of protein related to lipid homeostasis, liver X receptor α and apolipoprotein E, were decreased after PFNA administration. Exposure to PFNA also increased the activity of serum alanine aminotransferase in diabetic rats. In conclusion, this study discloses that exposure to PFNA impacts on enzymes and proteins related to liver lipid metabolism and lead to obvious accumulation of lipid in the liver of diabetic rats, which may be responsible for hepatotoxicity of this compound in individuals with diabetes mellitus.			●							-		C	C
1120	実験動物（反復投与毒性）	Fang, Xuemei; Wu, Chao; Li, Hongxia; Yuan, Weifeng; Wang, Xin	Elevation of intracellular calcium and oxidative stress is involved in perfluorononanoic acid-induced neurotoxicity	2018	Toxicol Ind Health. 2018 Mar;34(3):139-145. doi: 10.1177/0748233717742262. Epub 2017 Nov 29.	Perfluorononanoic acid (PFNA) is one of the major perfluorinated compounds found in both biological and abiotic samples and has recently been demonstrated to cause neurobehavioral defects in mammals. In this study, pheochromocytoma-12 (PC12) cells were exposed to various doses of PFNA to explore the cytotoxicity of PFNA to neurons and the possible mechanisms underlying these effects. The results showed that exposure to PFNA dose-dependently decreased the viability of PC12 cells and increased the release of lactate dehydrogenase into cell culture media. Exposure to PFNA increased the malondialdehyde content and decreased the total antioxidant capacity and glutathione peroxidase activity in PC12 cell culture supernatants. Exposure to PFNA increased the intracellular calcium level and upregulated the Ca(2+)/calmodulin-dependent protein kinase II (CaMKII) expression in PC12 cells. PFNA also decreased Bcl-2 expression and increased Bax expression in PC12 cells. These results suggested that exposure to PFNA elevated the intracellular calcium level and activated the CaMKII signaling pathway, which may aggravate oxidative stress in PC12 cells and lead to cell damage or cell apoptosis.			●							-		C	C
1121	実験動物（反復投与毒性）	Foreman, Jennifer E; Chang, Shu-Ching; Ehresman, David J; Butenhoff, John L; Anderson, Cherie R; Palkar, Prajakta S; Kang, Boo-Hyon; Gonzalez, Frank J; Peters, Jeffrey M	Differential hepatic effects of perfluorobutyrate mediated by mouse and human PPAR-alpha	2009	Toxicol Sci. 2009 Jul;110(1):204-11. doi: 10.1093/toxsci/kfp077. Epub 2009 Apr 9.	Perfluorobutyrate (PFBA) is a short chain perfluoroalkyl carboxylate that is structurally similar to perfluorooctanoate. Administration of PFBA can cause peroxisome proliferation, induction of peroxisomal fatty acid oxidation and hepatomegaly, suggesting that PFBA activates the nuclear receptor, peroxisome proliferator-activated receptor-alpha (PPAR-alpha). In this study, the role of PPAR-alpha in mediating the effects of PFBA was examined using PPAR-alpha null mice and a mouse line expressing the human PPAR-alpha in the absence of mouse PPAR-alpha (PPAR-alpha humanized mice). PFBA caused upregulation of known PPAR-alpha target genes that modulate lipid metabolism in wild-type and PPAR-alpha humanized mice, and this effect was not found in PPAR-alpha null mice. Increased liver weight and hepatocyte hypertrophy were also found in wild-type and humanized PPAR-alpha mice treated with PFBA, but not in PPAR-alpha null mice. Interestingly, hepatocyte focal necrosis with inflammatory cell infiltrate was only found in wild-type mice administered PFBA; this effect was markedly diminished in both PPAR-alpha null and PPAR-alpha humanized mice. Results from these studies demonstrate that PFBA can modulate gene expression and cause mild hepatomegaly and hepatocyte hypertrophy through a mechanism that requires PPAR-alpha and that these effects do not exhibit a species difference. In contrast, the PPAR-alpha-dependent increase in PFBA-induced hepatocyte focal necrosis with inflammatory cell infiltrate was mediated by the mouse PPAR-alpha but not the human PPAR-alpha. Collectively, these findings demonstrate that PFBA can activate both the mouse and human PPAR-alpha, but there is a species difference in the hepatotoxic response to this chemical.			●	●						-		C	C
1122	実験動物（反復投与毒性）	Frawley, Rachel P; Smith, Matthew; Cesta, Mark F; Hayes-Bouknight, Schantel; Blystone, Chad; Kissling, Grace E; Harris, Shawn; Germolec, Dori	Immunotoxic and hepatotoxic effects of perfluoro-n-decanoic acid (PFDA) on female Harlan Sprague-Dawley rats and B6C3F1/N mice when administered by oral gavage for 28 days	2018	J Immunotoxicol. 2018 Dec;15(1):41-52. doi: 10.1080/1547691X.2018.1445145.	Poly- and perfluoroalkyl substances (PFAS) are chemically and thermally stable, hydrophobic, lipophobic compounds used in stain repellants and water and oil surfactants, and associated with immunosuppression and peroxisome proliferator activity. Perfluoro-n-decanoic acid (PFDA, (CF(3)(CF(2))(8)COOH), a fluorinated straight chain fatty acid compound, is reported to induce thymic atrophy and reversible bone marrow hypocellularity in rodent models. The objective of this study was to assess potential immunotoxicity of PFDA, due to its structural similarity to other immunosuppressive PFASs. Female Harlan Sprague-Dawley rats were exposed to 0-2.0 mg PFDA/kg by oral gavage daily for 28 d. Female B(6)C(3)F(1)/N mice were exposed once/week to 0-5.0 mg PFDA/kg by gavage for 4 weeks. Animals were evaluated for effects on immune cell populations in spleen and bone marrow, and innate, humoral-, and cell-mediated immunity. Mice were also evaluated for resistance to Influenza virus. Treatment-related hepatocyte necrosis and hepatomegaly were observed in rats treated with 0.5 mg PFDA/kg/d. In mice, hepatomegaly (26-89%) was observed following exposure to ≥0.625 mg PFDA/kg/week, while splenic atrophy (20%) was observed at 5.0 mg PFDA/kg/week. At 5.0 mg PFDA/kg/week, total spleen cells, and Ig + and NK + cells were decreased (17.6-27%). At ≥ 1.25 mg PFDA/kg/week the numbers of splenic CD3(+), CD4(+), CD8(+), and Mac3(+) cells were decreased (10.5-39%). No changes were observed in leukocyte subpopulations in PFDA-exposed rats. Phagocytosis by fixed-tissue macrophages was decreased in liver (specific activity, 24-39%) at ≥0.25 mg PFDA/kg/d in rats. PFDA-induced effects on humoral- and cell-mediated immunity, host resistance, and bone marrow progenitor cells were limited. These data suggest that exposure to PFDA may induce adverse effects in rat liver in a manner consistent with the PFAS class, and may also alter the balance of immune cell populations in lymphoid tissues in mice.			●	●						-		C	C
1123	実験動物（反復投与毒性）	Hadrup, Niels; Pedersen, Mikael; Skov, Kasper; Hansen, Niels Lund; Berthelsen, Line Olrik; Kongsbak, Kristine; Boberg, Julie; Dybdahl, Marianne; Hass, Ulla; Frandsen, Henrik; Vinggaard, Anne Marie	Perfluorononanoic acid in combination with 14 chemicals exerts low-dose mixture effects in rats	2016	Arch Toxicol. 2016 Mar;90(3):661-75. doi: 10.1007/s00204-015-1452-6. Epub 2015 Jan 15.	Humans are simultaneously exposed to several chemicals that act jointly to induce mixture effects. At doses close to or higher than no-observed adverse effect levels, chemicals usually act additively in experimental studies. However, we are lacking knowledge on the importance of exposure to complex real-world mixtures at more relevant human exposure levels. We hypothesised that adverse mixture effects occur at doses approaching high-end human exposure levels. A mixture (Mix) of 14 chemicals at a combined dose of 2.5 mg/kg bw/day was tested in combination with perfluorononanoic acid (PFNA) at doses of 0.0125 (Low PFNA), 0.25 (Mid PFNA) and 5 (High PFNA) mg/kg bw/day by oral administration for 14 days in juvenile male rats. Indication of a toxicokinetic interaction was found, as simultaneous exposure to PFNA and the Mix caused a 2.8-fold increase in plasma PFNA concentrations at Low PFNA. An increase in testosterone and dihydrotestosterone plasma concentrations was observed for Low PFNA + Mix. This effect was considered non-monotonic, as higher doses did not cause this effect. Reduced LH plasma concentrations together with increased androgen concentrations indicate a disturbed pituitary-testis axis caused by the 15-chemical mixture. Low PFNA by itself increased the corticosterone plasma concentration, an effect which was normalised after simultaneous exposure to Mix. This combined with affected ACTH plasma concentrations and down-regulation of 11β HSD mRNA in livers indicates a disturbed pituitary-adrenal axis. In conclusion, our data suggest that mixtures of environmental chemicals at doses approaching high-end human exposure levels can cause a hormonal imbalance and disturb steroid hormones and their regulation. These effects may be non-monotonic and were observed at low doses. Whether this reflects a more general phenomenon that should be taken into consideration when predicting human mixture effects or represents a rarer phenomenon remains to be shown.			●	●						-		C	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報抽出対象	文献ランク①	文献ランク②
1124	実験動物（反復投与毒性）	Huck, Ian; Beggs, Kevin; Apte, Udayan	Paradoxical protective effect of perfluorooctanesulfonic acid against high-fat diet-induced hepatic steatosis in mice	2018	Int J Toxicol. 2018 Sep/Oct;37(5):383-392. doi: 10.1177/1091581818790934. Epub 2018 Aug 22.	Perfluorooctanesulfonic acid (PFOS) is a persistent organic pollutant with worldwide bioaccumulation due to a very long half-life. Perfluorooctanesulfonic acid exposure results in significant hepatic effects including steatosis, proliferation, hepatomegaly, and in rodents, carcinogenesis. The objective of this study was to determine whether PFOS exposure exacerbates nonalcoholic fatty liver disease and nonalcoholic steatohepatitis pathogenesis. Eight-week-old male C57BL/6 J mice (n = 5 per group) were fed ad libitum normal chow diet (ND) alone, 60% high-fat diet (HFD) alone, ND + PFOS, and HFD + PFOS (0.0001% w/w (1 mg/kg) of PFOS) for 6 weeks. Both HFD alone and the ND + PFOS treatment induced significant adiposity and hepatomegaly, but the HFD + PFOS treatment showed a marked protection. Oil Red O staining and quantitative analysis of hepatic lipid content revealed increased hepatic steatosis in ND + PFOS and in HFD alone fed mice, which was prevented in HFD + PFOS treatment. Further studies revealed that ND + PFOS treatment significantly affected expression of lipid trafficking genes to favor steatosis, but these changes were absent in HFD + PFOS group. Specifically, expression of CD36, the major lipid importer in the cells, and peroxisome proliferator-activated receptor gamma (PPAR γ), its major regulator, were induced in HFD + no treatment (NT) and ND + PFOS-fed mice but remained unchanged in HFD + PFOS mice. In conclusion, these data indicate that coadministration of PFOS with HFD mitigates steatosis and hepatomegaly induced by HFD and that by PFOS fed in ND diet via regulation of cellular lipid import machinery. These findings suggest dietary lipid content be considered when performing risk management of PFOS in humans and the elucidation of PFOS-induced hepatotoxicity.			●							-		B	B
1125	実験動物（反復投与毒性）	Hui, Zongguang; Li, Rujiang; Chen, Li	The impact of exposure to environmental contaminant on hepatocellular lipid metabolism	2017	Gene. 2017 Jul 30;622:67-71. doi: 10.1016/j.gene.2017.04.024. Epub 2017 Apr 19.	Increasing evidences show that ubiquitous perfluorooctanoic acid (PFOA), a representative environmental pollutant, is found to be linked to lipid dysmetabolism. However, the biological mechanism behind this outcome remains uninvestigated. In the present study, we established the PFOA-injured liver in mice to explore the underlying mechanism associated with PFOA-induced lipid disturbance in the liver via a group of biochemical and molecular assays. As results, PFOA-exposed mice showed increased transaminase (ALT), reduced triglyceride and free fatty acid contents in serum, as well as elevated level of hepatic triglyceride. Morphologically, PFOA-exposed mice displayed visible vacuolation in cytoplasm and abnormal cytoarchitecture in liver. In addition, PFOA-exposed liver showed up-regulated expressions of lipid-uptake associated mRNA of hepatic lipoprotein lipase (LPL) and fatty acid translocase (CD36) and down-regulated expression of lipid-uptake associated mRNA of apolipoprotein-B100 (APOB). Moreover, validated data from immunohistochemistry and immunoblotting found that hepatocellular LPL and CD36 proteins were increased dose-dependently, and lowered expression of hepatic APOB was observed. In conclusion, our current findings reveal that PFOA-induced lipid dysmetabolism in the liver is involved to dysregulation of fatty acid trafficking.			●							-		B	B
1126	実験動物（反復投与毒性）	Iwase, Yuko; Kudo, Naomi; Toyama, Tomoaki; Tamura, Masafumi; Mitsumoto, Atsushi; Kawashima, Yoichi	Effects of 8-2 fluorotelomer alcohol on oleic acid formation in the liver of rats	2006	Biol Pharm Bull. 2006 Aug;29(8):1740-6. doi: 10.1248/bpb.29.1740.	Effects of 8-2 fluorotelomer alcohol on fatty acid composition of lipid in the liver of rats were investigated. Feeding of male rats with a diet that contained 8-2 fluorotelomer alcohol at concentrations of 0.2, 0.4 and 0.8% (w/w) for 14 d caused a significant increase in proportion and content of oleic acid (18 : 1 (n-9)) in the liver. The treatment of rats with 8-2 fluorotelomer alcohol increased activities of palmitoyl-CoA chain elongase (PCE) and stearoyl-CoA desaturase (SCD) and mRNA expressions for rat fatty acid elongase 2 (rELO2) and stearoyl-CoA desaturase 1 (SCD1), but neither rat fatty acid elongase 1 (rELO1) or stearoyl-CoA desaturase 2 (SCD2), in the liver in dose-dependent manners. Multiple regression analyses, which were performed to estimate relative contribution of PCE and SCD for determination of the proportion or the content of 18 : 1 (n-9), revealed that the three parameters were significantly correlated and that standardized partial regression coefficient of PCE was higher than that of SCD. These results suggest that 8-2 fluorotelomer alcohol caused considerable changes in the composition and the content of fatty acid, especially 18 : 1 (n-9), in the liver by inducing PCE and SCD, and that PCE plays a crucial role in the increased proportion of 18 : 1 (n-9) in the liver of the rats given fluorotelomer alcohol.			●							-		C	C
1127	実験動物（肝毒性）	Kawashima, Y; Kobayashi, H; Miura, H; Kozuka, H	Characterization of hepatic responses of rat to administration of perfluorooctanoic and perfluorodecanoic acids at low levels	1995	Toxicology. 1995 May 23;99(3):169-78. doi: 10.1016/0300-483x(95)03027-d.	Male rats were fed a diet that contained perfluorooctanoic acid (PFOA) and perfluorodecanoic acid (PFDA) at concentrations ranging from 0.0025-0.04% (w/w) and from 0.00125-0.01% (w/w), respectively, for 1 week. The hepatic responses of the rats to PFOA and PFDA were examined. Upon the administration of PFOA and PFDA, three peroxisome proliferator-responsive parameters, peroxisomal beta-oxidation, microsomal 1-acylglycerophosphocholine (1-acyl-GPC) acyltransferase and cytosolic long-chain acyl-CoA hydrolase, were induced in a dose-dependent manner. A multiple regression analysis of the three parameters revealed that the data from rats treated with PFOA and PFDA shared one common line, indicating a marked correlation among the inductions of the three parameters. The activities of glutathione (GSH) S-transferases towards 1-chloro-2,4-dinitrobenzene (CDNB) and 1,2-dichloro-4-nitrobenzene (DCNB) were depressed by PFOA and PFDA. Significant inverse correlations were found between activities of GSH S-transferases and peroxisomal beta-oxidation. The administration of PFOA and PFDA significantly increased hepatic concentration of triacylglycerol. The perfluorocarboxylic acids at relatively high doses caused accumulation of cholesterol in liver. Electron microscopic studies showed that the administration of PFOA and PFDA caused an increase in cell size and proliferations of peroxisomes, and that the treatment of rats with PFDA at dietary concentration of 0.01% caused a marked increase in small lipid droplet in hepatocytes, indicative of hepatotoxic manifestations. The present results suggest that when PFOA and PFDA are administered at low levels, there are no differences between the properties of the perfluorocarboxylic acids as peroxisome proliferators, although the administration of PFDA at the doses exceeding a certain level becomes markedly toxic to hepatocytes.			●	●						-	1	B	A
1128	実験動物（反復投与毒性）	Kudo, N; Bandai, N; Suzuki, E; Katakura, M; Kawashima, Y	Induction by perfluorinated fatty acids with different carbon chain length of peroxisomal beta-oxidation in the liver of rats	2000	Chem Biol Interact. 2000 Jan 15;124(2):119-32. doi: 10.1016/s0009-2797(99)00150-7.	The potency of the induction of peroxisomal beta-oxidation was compared between perfluorinated fatty acids (PFCAs) with different carbon chain lengths in the liver of male and female rats. In male rats, perfluoroheptanoic acid (PFHA) has little effect, although perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA) and perfluorodecanoic acid (PFDA) potentially induced the activity. By contrast, PFHA and PFOA did not induce the activity of peroxisomal beta-oxidation in the liver of female rats while PFNA and PFDA effectively induced the activity. The induction of the activity by these PFCAs was in a dose-dependent manner, and there is a highly significant correlation between the induction and hepatic concentrations of PFCAs in the liver regardless of their carbon chain lengths. These results strongly suggest that the difference in their chemical structure is not the cause of the difference in the potency of the induction. Hepatic concentrations of PFOA and PFNA was markedly higher in male compared with female rats. Castration of male rats reduced the concentration of PFNA in the liver and treatment with testosterone entirely restored the reduction. In contrast to the results obtained from the in vivo experiments, the activity of peroxisomal beta-oxidation was induced by PFDA and PFOA to the same extent in cultured hepatocytes prepared from both male and female rats. These results, taken together, indicate that difference in accumulation between PFCAs in the liver was responsible for the different potency of the induction of peroxisomal beta-oxidation between PFCAs with different carbon chain lengths and between sexes.			●	●						-		B	B
1129	実験動物（反復投与毒性）	Kudo, Naomi; Suzuki-Nakajima, Erika; Mitsumoto, Atsushi; Kawashima, Yoichi	Responses of the liver to perfluorinated fatty acids with different carbon chain length in male and female mice	2006	Biol Pharm Bull. 2006 Sep;29(9):1952-7. doi: 10.1248/bpb.29.1952.	The potency of the induction of hepatomegaly, peroxisomal beta-oxidation and microsomal 1-acylglycerophoshocholine (1-acyl-GPC) acyltransferase was compared among perfluorinated fatty acids (PFCAs) with 6-9 carbon chain length in the liver of male and female mice. All PFCAs examined induced hepatomegaly and peroxisomal beta-oxidation and the potency was in the order of perfluorononanonic acid (PFNA), perfluorooctanoic acid (PFOA), perfluoroheptanoic acid (PFHA) and perfluorohexanoic acid (PFHeA) when compared with the relative doses to induce the two parameters. Microsomal 1-acyl-GPC acyltransferase was induced by PFHA, PFOA and PFNA, as was peroxisomal beta-oxidation. No significant sex-related difference was observed in the induction of peroxisomal beta-oxidation by any PFCAs examined. PFNA and PFOA accumulated in the liver of both male and female mice in a dose-dependent manner. PFHA accumulated in the liver to a lesser extent; little PFHeA accumulated in the liver. Hepatic concentrations of PFNA, PFOA and PFHA were higher in male mice than those in female mice. One linear regression line was confirmed between the activities of peroxisomal beta-oxidation and hepatic concentrations of PFHeA, PFHA, PFOA and PFNA in male mice regardless of their carbon chain lengths, and the activities were saturable at the concentrations over approximately 500 nmol/g liver. Similar linear regression line was obtained between the two parameters in female mice. These results suggest (i) that the longer the perfluoroalkyl chain becomes, the more PFCA accumulates in the liver of both male and female mice, (ii) that the accumulated PFCAs induce hepatomegaly, peroxisomal beta-oxidation and microsomal 1-acyl-GPC acyltransferase, and (iii) that the difference observed in the accumulation of PFHA, PFOA and PFNA in the liver between male and female mice is not enough to produce obvious sex-related difference in the induction of peroxisomal beta-oxidation.			●	●						-		B	B
1130	実験動物（反復投与毒性）	Ladics, Gregory S; Kennedy, Gerald L; O'Connor, John; Everds, Nancy; Malley, Linda A; Frame, Steven R; Gannon, Shawn; Jung, Reinhard; Roth, Thomas; Iwai, Hiroyuki; Shin-Ya, Seiji	90-day oral gavage toxicity study of 8-2 fluorotelomer alcohol in rats	2008	Drug Chem Toxicol. 2008;31(2):189-216. doi: 10.1080/01480540701873103.	8-2 fluorotelomer alcohol is a fluorinated chemical intermediate used to manufacture specialty polymers and surfactants. The potential subchronic toxicity and the reversibility of the effects of this chemical were evaluated following approximately 90 days of oral gavage dosing to Crl:CD(SD)IGS BR rats. A complete toxicological profile, including neurobehavioral assessments and hepatic beta-oxidation, were conducted at selected intervals and a group of rats was included for a 90-day postdosing recovery period. Dose levels tested were 0 (control), 1, 5, 25, and 125 mg/kg. No test-substance-related mortality occurred at any dose level. Rats at 125 mg/kg developed striated teeth, such that these animals were switched to ground chow at 77 days. No treatment-related alterations in body weight, food consumption, neurobehavioral parameters, or hematology/clinical chemistry were found. Hepatic beta-oxidation was increased in males at 125 mg/kg and in females at 25 and 125 mg/kg. In both males and females, plasma fluorine levels were increased at 125 mg/kg and urinary fluorine was elevated at > or =5 mg/kg. Degeneration/disorganization of enamel organ ameloblast cells was observed at 125 mg/kg in males, but not females. Liver weight increases accompanied by focal hepatic necrosis were observed at both 25 and 125 mg/kg, and chronic progressive nephrotoxicity occurred in female rats at 125 mg/kg. With the exception of hepatocellular necrosis in males at 125 mg/kg and the increased incidence and severity of chronic progressive nephropathy in females at 125 mg/kg, all other changes showed evidence of reversibility. The no-observed-adverse-effect level was 5 mg/kg.			●							-		C	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1131	実験動物（PPAR）	Li, Xilin; Wang, Zemin; Klaunig, James E	The effects of perfluorooctanoate on high fat diet induced non-alcoholic fatty liver disease in mice	2019	Toxicology. 2019 Mar 15;416:1-14. doi: 10.1016/j.tox.2019.01.017. Epub 2019 Jan 31.	Non-alcoholic fatty liver disease (NAFLD) is affecting up to one-third of the general population in western countries. While the major cause of NAFLD is related to an unhealthy lifestyle, recent evidence has shown a role of chemical exposure in the induction and progression of NAFLD. Perfluorooctanoate (PFOA) is a ubiquitous environmental contaminant that exerts its hepatotoxicity mainly through the activation of peroxisome proliferator-activated receptor α (PPARα). We examined how PFOA might affect the progression of NAFLD and whether a preexisting fatty liver intensified or alleviated the effects of PFOA in the livers. As such, male C57BL/6 mice were fed with a low-fat control diet (CD) or a high fat diet (HFD) for 16 weeks to model normal or steatotic livers, respectively. Mice were then administered with PFOA (1mg/kg/d) by oral gavage for an additional 2, 8, and 16 weeks. Dietary treatment was continued throughout the whole study. We found HFD induced hepatic steatosis, lobular inflammation, and progressive fibrosis in mice. As expected, PFOA activated PPARα, constitutive androstane receptor (CAR) and pregnane X receptor (PXR), regardless of the diet. Gene expression analysis showed the interactions between HFD and PFOA on hepatic nuclear receptors were time-dependent. Hepatocytes growth as measured by DNA synthesis and cell growth genes induced by PFOA were exacerbated in the HFD group after 2 weeks, along with the enhanced activation of PPARα. In contrast, PFOA decreased the severity of hepatic steatosis. In HFD-fed mice, the hepatic triglyceride levels were reduced to 75%, 47%, and 40%, after 2, 8, and 16 weeks of PFOA treatment, respectively, compared to vehicle controls. Transcriptomic analysis showed the preexisting NAFLD enhanced PFOA related lipid oxidation pathways in mice. HFD induced hepatic fibrosis as measured by collagen staining and fibrosis gene markers were also attenuated by PFOA. Taken together, this study demonstrated that the preexisting NAFLD might impact on many biological effects induced by PFOA and thus need to be carefully considered as a factor in risk assessment.			●							-	1	B	A
1132	実験動物（反復投与毒性）	Lieder, Paul H; Chang, Shu-Ching; York, Raymond G; Butenhoff, John L	Toxicological evaluation of potassium perfluorobutanesulfonate in a 90-day oral gavage study with Sprague-Dawley rats	2009	Toxicology. 2009 Jan 8;255(1-2):45-52. doi: 10.1016/j.tox.2008.10.002. Epub 2008 Oct 17.	Perfluorobutanesulfonate (PFBS) is a surfactant and degradation product of substances synthesized using perfluorobutanesulfonyl fluoride. A 90-day rat oral gavage study has been conducted with potassium PFBS (K+PFBS). Rats were dosed with K+PFBS at doses of 60, 200, and 600mg/kg-day body weight. The following endpoints were evaluated: clinical observations, food consumption, body weight, gross and microscopic pathology, clinical chemistry, and hematology. In addition, functional observation battery and motor activity assessments were made. Histological examination included tissues in control and 600 mg/kg-day groups. Additional histological examinations were performed on nasal cavities and turbinates, stomachs, and kidneys in the 60 and 200 mg/kg-day groups. No treatment-related mortality, body weight, or neurological effects were noted. Chromorhinorrhea (perioral) and urine-stained abdominal fur were observed in males at 600mg/kg-day. Red blood cell counts, hemoglobin, and hematocrit values were reduced in males receiving 200 and 600mg/kg-day; however, there were no adverse histopathological findings in bone marrow. Total protein and albumin were lower in females at 600mg/kg-day. There were no significant changes in clinical chemistry in either sex. All rats appeared normal at sacrifice. Microscopic changes were observed only at the highest dose in the stomach. These changes consisted of hyperplasia with some necrosis of the mucosa with some squamous metaplasia. These effects likely were due to a cumulative direct irritation effect resulting from oral dosing with K+PFBS. Histopathological changes were also observed in the kidneys. The changes observed were minimal-to-mild hyperplasia of the epithelial cells of the medullary and papillary tubules and the ducts in the inner medullary region. There were no corresponding changes in kidney weights. Clinical chemistry parameters related to kidney function were unchanged. These kidney findings are likely due to a response to high concentration of K+PFBS in tubules and ducts and represent a minimal-to-mild effect. Microscopic changes of an equivocal and uncertain nature were observed in the nasal mucosa and were likely attributable to the route of dosing (oral gavage). The NOAEL for the female rat in this study was 600 mg/kg-day (highest dose of study). The NOAEL for the male rat was 60 mg/kg-day based on hematological effects.			●	●						-		C	C
1133	実験動物（反復投与毒性）	Liu, Hui; Zhang, Hongxia; Cui, Ruina; Guo, Xuejiang; Wang, Dazhi; Dai, Jiayin	Activation of peroxisome proliferator-activated receptor a ameliorates perfluorododecanoic acid-induced production of reactive oxygen species in rat liver	2016	Arch Toxicol. 2016 Jun;90(6):1383-97. doi: 10.1007/s00204-015-1559-9. Epub 2015 Jul 14.	Perfluorododecanoic acid (PFDoA) is a ubiquitous environmental pollutant known to cause hepatocellular hypertrophy; however, the mechanisms of hepatotoxicity remain poorly understood. In this study, male rats were exposed to 0, 0.05, 0.2 and 0.5 mg/kg/day of PFDoA for 110 days. After two-dimensional differential gel electrophoresis and MALDI-TOF/TOF analysis, 73 differentially expressed proteins involved in lipid metabolism, inflammation, stress response and other functions were successfully identified. Among them, six significantly changed proteins (CTE1, MTE1, HADHA, ECH1, ALDH2 and CPS1) were found to be regulated by peroxisome proliferator-activated receptor alpha (PPARα). The anti-oxidant enzyme activity assays of superoxide dismutase and glutathione peroxidase and the content of thiobarbituric acid-reactive substances in the liver implied that PFDoA caused oxidative stress. The mRNA levels of PPARα in rat primary hepatocytes were knocked down by lentivirus-mediated RNAi. Furthermore, targeted protein levels of CTE1 and MTE1 were down-regulated, while those of HADHA, ALDH2 and CPS1 were up-regulated. After PFDoA exposure, however, the targeted protein levels of CTE1 and ALDH2 increased compared with those of the knockdown untreated group. The reactive oxygen species (ROS) content in rat hepatocytes assayed by flow cytometry significantly increased in the PPARα knockdown groups, consistent with the PPARα antagonist GW6471- and agonist WY14643-treated groups. These results strongly suggested that PPARα played an important role in suppressing ROS content in hepatocytes following PFDoA exposure.			●							-		C	C
1134	実験動物（心血管系）	Lv, Na; Zhao, Meng; Han, Yantao; Cui, Lianhua; Zhong, Weizhen; Wang, Chunbo; Jiang, Qixiao	The roles of bone morphogenetic protein 2 in perfluorooctanoic acid induced developmental cardiotoxicity and l-carnitine mediated protection	2018	Toxicol Appl Pharmacol. 2018 Aug 1;352:68-76. doi: 10.1016/j.taap.2018.05.028. Epub 2018 May 23.	Perfluorooctanoic acid (PFOA), a wide spread environmental pollutant, was associated with developmental cardiotoxicity in chicken embryo, while the underlying molecular mechanism had not been fully elucidated. In the current study, 2 mg/kg (egg weight) PFOA and/or 100 mg/kg (egg weight) l-carnitine were exposed to embryonic day zero (ED0) chicken embryo via air cell injection, and then bone morphogenic protein 2 (BMP2) silencing lentivirus or BMP2 recombinant protein were introduced into ED2 embryo. Electrocardiography and histological methods were utilized to assess the cardiac function and morphology in hatchling chickens, respectively. Consistent with previous results, 2 mg/kg PFOA exposure at ED0 significantly elevated heart rate and thinned right ventricular wall in hatchling chickens, while l-carnitine co-treatment reverted such changes. BMP2 silencing induced very similar changes in hatchling chicken hearts as PFOA exposure, while co-exposure of recombinant BMP2 protein alleviated PFOA-induced changes. l-carnitine exposure alleviated the BMP2-silencing induced changes as well. Western blotting revealed that PFOA exposure enhanced BMP2 expression and suppressed pSMAD1 expression in ED15 chicken embryo hearts, while both changes were reverted by l-carnitine co-exposure. Furthermore, silencing of BMP2 significantly increased the expression level of PPAR alpha in ED15 chicken embryo hearts, while silencing of PPAR alpha did not have significant impact on BMP2 expression. In conclusion, BMP2/pSMAD1 signaling participates in the PFOA-induced developmental cardiotoxicity in chicken embryo, which is likely located upstream of PPAR alpha for this particular endpoint. Protection of BMP2 signaling might contribute to l-carnitine mediated protection against PFOA-induced developmental cardiotoxicity.			●							-	1	B	A
1135	実験動物（反復投与毒性）	NICNAS	Potassium perfluorobutane sulfonate: Hazard assessment	2005	Available at https://www.informea.org/sites/default/files/imported-documents/UNEP-POPS-POPRC12FU-SUBM-PFOA-Canada-34-20161209.En.pdf	No abstract available			●						評価書		D	D
1136	実験動物（反復投与毒性）	Rosen, Mitchell B; Das, Kaberi P; Rooney, John; Abbott, Barbara; Lau, Christopher; Corton, J Christopher	PPARalpha-independent transcriptional targets of perfluoroalkyl acids revealed by transcript profiling	2017	Toxicology. 2017 Jul 15;387:95-107. doi: 10.1016/j.tox.2017.05.013. Epub 2017 May 27.	Perfluoroalkyl acids (PFAAs) are ubiquitous and persistent environmental contaminants. Compounds such as perfluoroocanoic acid (PFOA), perfluorooctane sulfonate (PFOS), perfluorononanoic acid (PFNA), and perfluorohexane sulfonate (PFHxS) are readily found in the tissues of humans and wildlife. While PFOA and PFOS have been the subject of numerous studies since they were first described over a decade ago, less is known about the biological activity of PFHxS and PFNA. Most PFAAs are activators of peroxisome proliferator-activated receptor α (PPARα), although the biological effects of these compounds are likely mediated by other factors in addition to PPARα. To evaluate the effects of PFHxS and PFNA, male wild-type and Pparα-null mice were dosed by oral gavage with PFHxS (3 or 10mg/kg/day), PFNA (1 or 3mg/kg/day), or vehicle for 7days, and liver gene expression was evaluated by full-genome microarrays. Gene expression patterns were then compared to historical in-house data for PFOA and PFOS in addition to the experimental hypolipidemic agent, WY-14,643. While WY-14,643 altered most genes in a PPARα-dependent manner, approximately 11-24% of regulated genes in PFAA-treated mice were independent of PPARα. The possibility that PFAAs regulate gene expression through other molecular pathways was evaluated. Using data available through a microarray database, PFAA gene expression profiles were found to exhibit significant similarity to profiles from mouse tissues exposed to agonists of the constitutive activated receptor (CAR), estrogen receptor α (ERα), and PPARγ. Human PPARγ and ERα were activated by all four PFAAs in trans-activation assays from the ToxCast screening program. Predictive gene expression biomarkers showed that PFAAs activate CAR in both genotypes and cause feminization of the liver transcriptome through suppression of signal transducer and activator of transcription 5B (STAT5B). These results indicate that, in addition to activating PPARα as a primary target, PFAAs also have the potential to activate CAR, PPARγ, and ERα as well as suppress STAT5B.			●	●						-		B	B
1137	実験動物（反復投与毒性）	Su, Min; Liang, Xiaoliu; Xu, Xiaoxiao; Wu, Xinmou; Yang, Bin	Hepatoprotective benefits of vitamin C against perfluorooctane sulfonate induced liver damage in mice through suppressing inflammatory reaction and ER stress	2019	Environ Toxicol Pharmacol. 2019 Jan;65:60-65. doi: 10.1016/j.etap.2018.12.004. Epub 2018 Dec 5.	Our previous studies show that vitamin C (VC) plays promising hepatoprotection in mice. Intrahepatic exposure of perfluorooctane sulfonate (PFOS) can induce dose-dependent cytotoxicity. However, pharmacology-based assessment of VC on PFOS remains uninvestigated. This study aimed to evaluate the therapeutic benefits of VC on inhibiting PFOS-induced liver steatosis in mice, followed by representative biochemical analysis and immunoassay. As results, VC was beneficial for reduced PFOS-induced liver damages, as showed in reductions of serological levels of transaminases (ALT and AST), lipids (TG and TC), fasting glucose and insulin, inflammatory cytokines (TNF-α and IL6), while content of fibroblast growth factor 21 (FGF21) in serum was increased. In addition, VC reduced histiocytic changes of PFOS-lesioned livers, as revealed in reduced TNF-α-labeled cells and increased FGF21-labeled cells in immunofluorescence assay. Further, intrahepatic expressions of endoplasmic reticulum (ER) stress-based ATF6, eIF2α, GRP78, XBP1 proteins were down-regulated by treatments of VC. Taken together, our preliminary findings set forth that VC exerts pharmacological benefits against PFOS-induced liver steatosis in mice, and the underlying biological mechanism may be linked to suppressing hepatocellular inflammatory reaction and ER stress.			●							-		C	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1138	実験動物（反復投与毒性）	Wang, Jianshe; Yan, Shengmin; Zhang, Wei; Zhang, Hongxia; Dai, Jiayin	Integrated proteomic and miRNA transcriptional analysis reveals the hepatotoxicity mechanism of PFNA exposure in mice	2015	J Proteome Res. 2015 Jan 2;14(1):330-41. doi: 10.1021/pr500641b. Epub 2014 Sep 24.	Perfluoroalkyl chemicals (PFASs) are a class of highly stable man-made compounds, and their toxicological impacts are currently of worldwide concern. Administration of perfluorononanoic acid (PFNA), a perfluorocarboxylic acid (PFCA) with a nine carbon backbone, resulted in dose-dependent hepatomegaly in mice (0, 0.2, 1, and 5 mg/kg body weight, once a day for 14 days) and an increase in hepatic triglycerides (TG) and total cholesterol (TCHO) in the median dose group as well as serum transaminases in the high dose group. Using isobaric tags for relative and absolute quantitation (iTRAQ), we identified 108 (80 up-regulated, 28 down-regulated) and 342 hepatic proteins (179 up-regulated, 163 down-regulated) that exhibited statistically significant changes (at least a 1.2-fold alteration and P < 0.05) in the 1 and 5 mg/kg/d PFNA treatment groups, respectively. Sixty-six proteins (54 up-regulated, 12 down-regulated) significantly changed in both of the two treatment groups. Among these 54 up-regulated proteins, most were proteins related to the lipid metabolism process (31 proteins). The mRNA analysis results further suggested that PFNA exposure not only resulted in a fatty acid oxidation effect but also activated mouse liver genes involved in fatty acid and cholesterol synthesis. Additionally, three (2 down-regulated, 1 up-regulated) and 30 (14 down-regulated, 16 up-regulated) microRNAs (miRNAs) exhibited at least a 2-fold alteration (P < 0.05) in the 1 and 5 mg/kg/d PFNA treatment groups, respectively, Three miRNAs (up-regulated: miR-34a; down-regulated: miR-362-3p and miR-338-3p) significantly changed in both of the two treatment groups. The repression effect of miR-34a on fucosyltransferase 8 (Fut8) and lactate dehydrogenase (Ldha) was confirmed by luciferase activity assay and Western blot analysis. The results implied that PFNA exerted a hepatic effect, at least partially, by miRNAs mediated post-translational protein repression.			●	●						-		C	C
1139	実験動物（反復投与毒性）	Wang, Li; Zhao, Fenglian; Kan, Mengying; Wen, Zhaoyan; Zhou, Yongbing; Yu, Lili; Liu, Hui	Effects of perfluorooctanoic acid on oxidative stress and PPARa and its related CYP4A1 gene expression in rat liver	2017	Wei Sheng Yan Jiu. 2017 Sep;46(5):802-806.	OBJECTIVE: To study the effects on oxidative stress and the expression of PPARα-related genes and protein in the liver of rats induced by pentadecafluorooctanoic acid(PFOA). METHODS: A total of 28 male SD rats were randomly divided into four groups: control group: double distilled water, low dose group: PFOA 1 mg/(kg·d), middle dose group: PFOA 5 mg/(kg·d), high dose group: PFOA 25 mg/(kg·d), and were administrated by gavage once a day for 14 days take the organization after anesthesia, according to the follow-up experiments need treatment. The activity of oxidative stressrelated enzymes and the content of malondialdehyde(MDA) in liver tissue were detected. The mRNA levels of peroxisome proliferators-activited receptors α(PPARα) and cytochrome P4504A1(CYP4A1) were detected by real-time PCR. The protein expression of PPARα was detected by Western blot. RESULTS: There was significant difference between high dose group and control group of the body weight(P < 0. 05). The liver weight and relative liver weight of the middle and high dose groups were significantly higher than those of the control group(P < 0. 05). The activity of superoxide dismutase(SOD) and glutathione peroxidase(GSH-Px) in the liver of the low dose group were significantly higher than that of the control group(P < 0. 05). The content of MDA in liver of middle and high dose groups were increased by 2. 5 times and 3. 5 times compared with that of control group(P < 0. 05). The expression of PPARα and its regulated CYP4A1 mRNA were significantly increased in low, middle and high dose groups. The expression of PPARα protein in the low, middle and high dose groups were up-regulated. CONCLUSION: PFOA exposure can lead to oxidative stress in rat liver, resulting in antioxidant enzymes SOD and GSH-Px and MDA changes. At the same time, PFOA exposure induced up regulation of PPARα and CYP4A1 in the liver of rats to enhance theβ-oxidation of fatty acids, leading to lipid peroxidation, which has obvious toxic effects on rat liver.			●							-		B	B
1140	実験動物（反復投与毒性）	Wang, Xia; Kong, Baida; He, Bingnan; Wei, Lai; Zhu, Jianbo; Jin, Yuanxiang; Shan, Yudong; Wang, Weitao; Pan, Chunqiang; Fu, Zhengwei	8:2 Fluorotelomer alcohol causes immunotoxicity and liver injury in adult male C57BL/6 mice	2019	Environ Toxicol. 2019 Feb;34(2):141-149. doi: 10.1002/tox.22668. Epub 2018 Dec 7.	8:2 Fluorotelomer alcohol (8:2 FTOH) is widely used in houseware and industrial goods and is ubiquitous in the surrounding environment. 8:2 FTOH has been linked to hepatoxicity, nephrotoxicity, and reproductive toxicity, as well as endocrine-disrupting effects. However, as of yet, the research regarding immunotoxicity of 8:2 FTOH remains largely limited. In the present study, adult male C57BL/6 mice were administered with 10, 30, and 100 mg/kg/d 8:2 FTOH by gavage for 28 days to investigate its immunotoxicity in vivo. The results showed that exposure to 8:2 FTOH caused increases in liver weight and histological changes in the liver, including vacuolation, cell swelling, immune cell infiltration, karyopyknosis and nuclear swelling. No histological change in either the spleen or the thymus was observed after administration of 8:2 FTOH. In addition, exposure to 8:2 FTOH reduced the concentration of IL-1β in serum, and mRNA levels of IL-1β, IL-6, and TNF-α in both the thymus and spleen. CXCL-1 mRNA expression was downregulated in both the liver and thymus after 8:2 FTOH administration, while only IL-1β mRNA expression was upregulated in the liver. Moreover, the exposure of primary cultured splenocytes to 8:2 FTOH inhibited the ConA-stimulated proliferation of splenocytes at concentrations of 30 and 100 μM, and the LPS-stimulated proliferation of splenocytes at 100 μM. Furthermore, 8:2 FTOH inhibited the level of secreted IFN-γ in ConA-stimulated splenocytes. The results obtained in the study demonstrated that 8:2 FTOH posed potential immunotoxicity and liver injury in mice. Our findings will provide novel data for the health risk assessment of 8:2 FTOH.			●							-		C	C
1141	実験動物（反復投与毒性）	Kirkpatrick, JB	A combined 28-day repeated dose oral toxicity study with the reproduction/ developmental toxicity screening test of perfluorohexanoic acid and 1H, 1H, 2H, 2H-tridecafluoro-1-octanol in rats, with recovery	2005	WIL Research Laboratories	No abstract available			●	●					企業データ		D	D
1142	実験動物（肝毒性）	Wu, Xinmou; Xie, Guojie; Xu, Xiaoxiao; Wu, Wei; Yang, Bin	Adverse bioeffect of perfluorooctanoic acid on liver metabolic function in mice	2018	Environ Sci Pollut Res Int. 2018 Feb;25(5):4787-4793. doi: 10.1007/s11356-017-0872-7. Epub 2017 Dec 2.	Perfluorooctanoic acid (PFOA), a kind of manufactured material, is widely accumulated around environmental system and into wildlife, including human beings. Toxicologically, PFOA induces hepatomegaly (liver enlargement) in the dose- and time-dependent manners. However, biological mechanism of hepatotoxicity warrants to be further investigated. In the present study, mature male mice were exposed to dosed PFOA for 21 days before conducting biochemical tests and immunoassays. As results, decreased fast blood glucose and elevated insulin contents were observed in PFOA-dosed mice. In addition, PFOA-dosed mice resulted in increased liver functional enzymes (GPT, GOT) in serum. And lipid contents (TG, lipoproteins) in serum and liver were changed abnormally. As shown in immunohistochemistry, increased insulin- and poly (ADP-ribose) polymerase (PARP)-positive cells were showed in PFOA-exposed pancreatic tissues. Moreover, CD36-positive cells were increased in PFOA-exposed livers, while ApoB-labeled cells were reduced. Further, immunoblot data showed that hepatocellular fibroblast growth factor 21 (FGF21) in PFOA-exposed liver was down-regulated dose-dependently. Taken together, our preliminary findings demonstrated that PFOA-induced hepatocellular lipotoxicity may be linked to impairing lipid-regulated proteins, as well as inducing insulin expression from pancreatic tissue.			●							-	1	B	A
1143	実験動物（反復投与毒性）	Zhang, Hongxia; Shi, Zhimin; Liu, Yang; Wei, Yanhong; Dai, Jiayin	Lipid homeostasis and oxidative stress in the liver of male rats exposed to perfluorododecanoic acid	2008	Toxicol Appl Pharmacol. 2008 Feb 15;227(1):16-25. doi: 10.1016/j.taap.2007.09.026. Epub 2007 Oct 6.	Perfluorododecanoic acid (PFDoA), a perfluorinated carboxylic acid (PFCA) with twelve carbon atoms, has broad industrial applications and is widely distributed in both wildlife and the environment. Unlike other PFCAs with short carbon chain, however, limited studies have been performed to date on the toxic effects of PFDoA on animals. To determine the hepatotoxicity of PFDoA, male rats were orally dosed by gavage for 14 days with 0, 1, 5, or 10 mg PFDoA/kg/day. Absolute liver weights were diminished, but the relative liver weight was significantly increased in the 5 and 10 mg PFDoA/kg/day groups. Meanwhile, serum triglyceride (TG) concentrations were decreased significantly in rats dosed with 1 and 5 mg PFDoA/kg/day, while the liver lipid accumulation was observed in ultrastructure. The expression of peroxisome proliferator-activated receptor (PPAR)-alpha and its target genes, and to a lesser extent PPARgamma, was induced by PFDoA. No significant changes in the expression of liver X receptor alpha (LXRalpha) or its target genes CYP7A1 and acetyl-CoA carboxylase 1 (ACC1) were noted, although the mRNA levels of several genes involved in lipogenesis and lipid transport were changed significantly in the certain of the experimental groups. In addition, superoxide dismutase (SOD) and catalase (CAT) activities were activated significantly in the 1 mg PFDoA/kg/day group and inhibited significantly with a concomitant increase of lipid peroxidation (LPO) levels in the 5 and 10 mg PFDoA/kg/day groups. Our results demonstrate that PFDoA exerts notable hepatotoxicity in male rats and that PPAR and its target genes, SOD and CAT activity, and LPO levels exhibited sensitivity to the toxicity of PFDoA.			●	●						-		C	C
1144	実験動物（反復投与毒性）	Zhang, Hongxia; Ding, Lina; Fang, Xuemei; Shi, Zhimin; Zhang, Yating; Chen, Hebing; Yan, Xianzhong; Dai, Jiayin	Biological responses to perfluorododecanoic acid exposure in rat kidneys as determined by integrated proteomic and metabonomic studies	2011	PLoS One. 2011;6(6):e20862. doi: 10.1371/journal.pone.0020862. Epub 2011 Jun 3.	BACKGROUND: Perfluorododecanoic acid (PFDoA) is a perfluorinated carboxylic chemical (PFC) that has broad applications and distribution in the environment. While many studies have focused on hepatotoxicity, immunotoxicity, and reproductive toxicity of PFCAs, few have investigated renal toxicity. METHODOLOGY/PRINCIPAL FINDINGS: Here, we used comparative proteomic and metabonomic technologies to provide a global perspective on renal response to PFDoA. Male rats were exposed to 0, 0.05, 0.2, and 0.5 mg/kg/day of PFDoA for 110 days. After 2-D DIGE and MALDI TOF/TOF analysis, 79 differentially expressed proteins between the control and the PFDoA treated rats (0.2 and 0.5 mg-dosed groups) were successfully identified. These proteins were mainly involved in amino acid metabolism, the tricarboxylic acid cycle, gluconeogenesis, glycolysis, electron transport, and stress response. Nuclear magnetic resonance-based metabonomic analysis showed an increase in pyruvate, lactate, acetate, choline, and a variety of amino acids in the highest dose group. Furthermore, the profiles of free amino acids in the PFDoA treated groups were investigated quantitatively by high-coverage quantitative iTRAQ-LC MS/MS, which showed levels of sarcosine, asparagine, histidine, 1-methylhistidine, Ile, Leu, Val, Trp, Tyr, Phe, Cys, and Met increased markedly in the 0.5 mg dosed group, while homocitrulline, α-aminoadipic acid, β-alanine, and cystathionine decreased. CONCLUSION/SIGNIFICANCE: These observations provide evidence that disorders in glucose and amino acid metabolism may contribute to PFDoA nephrotoxicity. Additionally, α(2u) globulin may play an important role in protecting the kidneys from PFDoA toxicity.			●							-		D	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ラン①抽出	文献ラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1145	実験動物（反復投与毒性）	Zhang, Hongxia; Hou, Junjie; Cui, Ruina; Guo, Xuejiang; Shi, Zhimin; Yang, Fuquan; Dai, Jiayin	Phosphoproteome analysis reveals an important role for glycogen synthase kinase-3 in perfluorododecanoic acid-induced rat liver toxicity	2013	Toxicol Lett. 2013 Mar 27;218(1):61-9. doi: 10.1016/j.toxlet.2013.01.012. Epub 2013 Jan 24.	Perfluorododecanoic acid (PFDoA) is a member of the perfluoroalkyl acid (PFAA) family and has broad applications and a wide distribution in the environment. Here, we used TiO(2)-based phosphopeptide enrichment coupled with LC-MS/MS analysis to identify phosphopeptides in rat livers that were influenced by PFDoA treatment. We identified a total of 1443 unique phosphopeptides from among 769 phosphoproteins identified in normal and PFDoA-treated rat livers, 849 unique phosphorylation sites were also identified. Of these sites, 143 were considered to be novel phosphorylation sites. Many phosphoproteins were found to be associated with hepatic injuries and diseases, such as hepatotoxicity, regeneration, fatty liver, neoplasms and carcinoma. Furthermore, 25 of the identified phosphoproteins were found to be related to glycogen synthase kinase-3 (GSK3), either directly or indirectly. Western blot and qPCR results suggested that chronic PFDoA exposure inhibited insulin signal pathways and that inhibition of GSK3 might contribute to the observed increases of lipid levels in the liver.			●							-		C	C
1146	実験動物（反復投与毒性）	Zhou, Xiangyu; Dong, Tianyi; Fan, Ziyan; Peng, Yanping; Zhou, Rongbin; Wang, Xiaqiong; Song, Ning; Han, Mingyong; Fan, Bingbing; Jia, Jihui; Liu, Shili	Perfluorodecanoic acid stimulates NLRP3 inflammasome assembly in gastric cells	2017	Sci Rep. 2017 Apr 3;7:45468. doi: 10.1038/srep45468.	Perfluorodecanoic acid (PFDA), a perfluorinated carboxylic acid, presents in the environment and accumulates in human blood and organs, but its association with tumor promotion are not clear. Given that inflammation plays a significant role in the development of gastric malignancies, we evaluated the effects of PFDA on activation of the inflammasome and inflammation regulation in the gastric cell line AGS. When added to cell cultures, PFDA significantly stimulated IL-1β and IL18 secretion and their mRNA levels compared with control cells. By RT-PCR and western-blot we found that up-regulation of NLRP3 were associated with promotion of IL-1β and IL-18 production. Then expression variation of cIAP1/2, c-Rel and p52 were analyzed, the results demonstrated raised mRNA expression in all the tested genes concomitant with enhanced inflammasome activity after exposure to PFDA. Assays with cIAP2 siRNA and NFκB reporter provided additional evidence that these genes were involved in PFDA-induced inflammasome assembly. Furthermore, increased secretion of IL-1β and IL-18 were detected in stomach of PFDA-treated mice, disorganized alignment of epithelial cells and inflammatory cell infiltration were also observed in the stomach tissues upon PFDA treatment. This study reports for the first time that PFDA regulates inflammasome assembly in human cells and mice tissues.			●							-		C	C
1147	実験動物（反復投与毒性）	3M	A 28-day oral (gavage) toxicity study of T-7485 in Sprague-Dawley rats	2001	St Paul, MN: 3M Corporate Toxicology.	No abstract available				●					企業データ		D	D
1148	実験動物（反復投与毒性）	3M	A 5-day repeat dose oral toxicity screening study in rats with a 7-day recovery period withMTDID	2007	St. Paul, MN: 3M Corporate Toxicology.	No abstract available				●					企業データ		D	D
1149	実験動物（反復投与毒性）	George, M E; Andersen, M E	Toxic effects of nonadecafluoro-n-decanoic acid in rats	1986	Toxicol Appl Pharmacol. 1986 Sep 15;85(2):169-80. doi: 10.1016/0041-008x(86)90110-9.	Nonadecafluoro-n-decanoic acid (ND-FDA) has a single dose ip LD50 of 41 mg/kg and causes anorexia and a wasting syndrome. NDFDA also appears to affect lipid metabolism although the metabolic fate and mechanism of action are not known. Control rats were pair fed with rats given 50 mg/kg. Body weights and food consumption were measured daily; body and organ weights, tissue histopathology, and hematological and clinical chemistry parameters were determined at 4, 8, 12, 16, and 30 days postdosing. Liver samples were obtained for determining cholesterol, cholesterol esters, phospholipids, total lipids, fatty acid ratios, and NDFDA. The rats became anorectic within 4 days and did not resume feeding for 10-12 days, losing about 40% of their body weight. There was a decrease in serum protein; total liver protein decreased and there was an increase in measured fatty acids except for stearic. Liver to body weight ratios of dosed rats were twice those of control rats since absolute liver weights in dosed rats remained constant during the weight loss period. The most striking histopathological change was seen in the liver with a uniform persistent cellular swelling at all times. Separation of the lipids by thin layer chromatography indicated that NDFDA was present in the most polar fraction. There also were fatty changes in the proximal tubular epithelium of the kidneys.				●						-		C	C
1150	実験動物（肝毒性）	Griffith, F D; Long, J E	Animal toxicity studies with ammonium perfluorooctanoate	1980	Am Ind Hyg Assoc J. 1980 Aug;41(8):576-83. doi: 10.1080/15298668091425301.	These studies were conducted to evaluate the potential toxicity of ammonium perfluorooctanoate, a commercial surfactant. They include acute and subchronic feeding studies with rabbits, mice, rats and monkeys as well as in vitro mutagenicity assays with Salmonella typhimurium and Saccharomyces cerevisiae. The compound was non-irritating to the skin and moderately irritating to the eyes of rabbits. The rat oral LD50 was 540 mg/kg; no deaths resulted from a one hour rat inhalation exposure at a nominal concentration of 18.6 mg/L. All in vitro assays were negative. The liver was the target organ in rodents in both the 28 day and 90 day feeding studies with males showing a greater response than females. Serum and liver concentrations of organic fluorine were greater in male than in female rats. In a 90 day oral study in rhesus monkeys the gastrointestinal tract and the reticuloendothelial system were the sites of toxic effects. The gastrointestinal effects were attributed to the potent surface activity of the compound. Histopathological effects wer noted in the spleen, lymph nodes and bone marrow. Unlike the rats, sex related differences were not evident in the monkeys. Toxicological evaluations of ammonium perfluorooctanoate are continuing.				●		●			●	-	1	A	A
1151	実験動物（腎毒性）	Hanhijärvi, H; Ylinen, M; Kojo, A; Kosma, V M	Elimination and toxicity of perfluorooctanoic acid during subchronic administration in the Wistar rat	1987	Pharmacol Toxicol. 1987 Jul;61(1):66-8. doi: 10.1111/j.1600-0773.1987.tb01775.x.	Perfluorinated fatty acids have been used commercially as corrosion inhibitors, wetting agents, fire extinguishers and surface active agents. In an earlier study the male rats were more susceptible to the toxic effects of perfluorooctanoic acid (PFO) than females. PFO-concentrations in the plasma suggested that there was a sex related difference in the urinary elimination rate. Active tubular secretion was observed only in the female kidney. The aim of the present study was to compare the urinary elimination of PFO between the two sexes during subchronic administration to the Wistar rat. PFO was administered by gavage to 48 newly-weaned animals at 0 mg/kg, 3 mg/kg, 10 mg/kg and 30 mg/kg for 28 consecutive days. The urine was collected on the 7th and 28th day of the study. At the end of the study, blood was collected by cardiac puncture. At necropsy, tissue specimens for histopathologic examination were collected from the controls and from the group receiving 30 mg/kg of PFO daily. Unlike the female rats, on the 7th day of the study all three groups of male rats excreted significant less PFO than their daily dose of PFO, which suggested that the males had not reached a steady state by seven days. On the 28th day, the males excreted an amount of PFO equal to their daily dose. The PFO concentrations in the plasma of the male animals suggested that the binding sites of PFO may become saturated at the chronic daily dose level of 30 mg/kg.(ABSTRACT TRUNCATED AT 250 WORDS)				●						-	1	B	A
1152	実験動物（反復投与毒性）	Iwai, Hiroyuki; Yamashita, Kotaro	A fourteen-day repeated dose oral toxicity study of APFO in rats	2006	Drug Chem Toxicol. 2006;29(3):323-32. doi: 10.1080/01480540600653143.	Ammonium perfluoroocanoate (APFO) was repeatedly administered orally to male Crj:CD(SD)IGS rats for 14 days. Doses of APFO were 0, 0.5, 5, and 50 mg/kg. Significant increases and increasing tendencies in absolute/relative weight of the liver and no change in weight of the spleen were observed in all groups. Although inductions of mitochondrion- and peroxisome-specific enzymes were increased, no decrease was seen in any hematological parameter of lipid metabolism. Red blood cell count, hemoglobin concentration, and hematocrit or these tendencies showed a significant decrease or a tendency to decrease, but no influence on lymphocyte subsets was noted. Secondary inhibition of immunocompetent cells, previously reported for mice, was not seen in this study of rats.				●						-		C	B
1153	実験動物（反復投与毒性）	Seacat AM, Luebker DJ.	Toxicokinetic study of perfluorooctane sulfonamide (PFOS; T-7132	2000	Submitted to the U.S. Environmental Protection Agency's Administrative Record. AR226-1030A011.	No abstract available				●					Administrative Record. AR226-1030A011.で検索したが入手不可		D	D
1154	実験動物（反復投与毒性）	Thomford PJ.	4-Week capsule toxicity study with ammonium perfluorooctanoate (APFO) in Cynomolgus monkeys	2001	APME Ad-Hoc APFO toxicology working group.	No abstract available				●		●			企業データ		D	D
1155	実験動物（反復投与毒性）	Thomford PJ.	4-week capsule toxicity study with perfluorooctane sulfonic acid potassium salt (PFOS; T-6295) in Cynomolgus monkeys	2002	St. Paul, MN: 3M.	No abstract available				●					企業データ		D	D
1156	実験動物（反復投与毒性）	van Otterdijk FM.	Repeated dose 28-day oral toxicity study with MTDID-8391 by daily gavage in the rat, followed by a 21-day recovery period	2007	3M.	No abstract available				●					企業データ		D	D
1157	実験動物（反復投与毒性）	van Otterdijk FM.	Repeated dose 90-day oral toxicity study with MTDID 8391 by daily gavage in the rat followed by a 3-week recovery period	2007	3M.	No abstract available				●					企業データ		D	D
1158	実験動物（反復投与毒性）	York R.	Oral (gavage) repeated dose 90-day toxicity study of potassium perfluorobutane sulfonate (PFBS) in rats	2003	Sponsor's Study Number: T-7485.15. Argus Research, Horsham, Pennsylvania.	No abstract available				●					企業データ		D	D
1159	実験動物（反復投与毒性）	NTP	NTP technical report on the toxicity studies of perfluoroalkyl carboxylates (perfluorohexanoic acid, perfluorooctanoic acid, perfluorononanoic acid, and perfluorodecanoic acid) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats [NTP]	2019	NTP. (Toxicity Report 97). Research Triangle Park, NC.	No abstract available	●	●	●						NTP TR（No.1341と重複、削除予定）		D	D

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1160	実験動物（PPAR）	Asakawa, Akihiro; Toyoshima, Megumi; Harada, Kouji H; Fujimiya, Mineko; Inoue, Kayoko; Koizumi, Akio	The ubiquitous environmental pollutant perfluorooctanoicacid inhibits feeding behavior via peroxisome proliferator-activated receptor-alpha	2008	Int J Mol Med. 2008 Apr;21(4):439-45. doi: 10.3892/ijmm.21.4.439	Perfluorinated compounds (PFCs) have been employed as surface treatment agents in a variety of products. Perfluorooctanoic acid (PFOA), a PFC that is found globally in the environment and in human tissues, has been increasing significantly in serum levels over the past 50 years. Here, we demonstrated that PFOA inhibits feeding behavior as potently as the endogenous peroxisome proliferator-activated receptor (PPAR)-alpha ligand, oleoylethanolamide (OEA), via the activation of PPAR-alpha, the vagal nerve and hypothalamic neuropeptides. Peripherally administered PFOA decreased food intake as potently as OEA. PFOA decreased gastric emptying and increased the expression level of the gene encoding urocortin 1 in the hypothalamus and the immunoreaction for urocortin 1 in the paraventricular nucleus. Vagotomy attenuated the inhibitory effects of PFOA on feeding. The inhibition of food intake and body-weight gain by PFOA was completely mitigated in PPAR-alpha-/-mice. Our studies demonstrated that the ubiquitous environmental pollutant PFOA works as an imitator of OEA mimicking its action in the feeding regulatory system, providing a new mode of action as represented by environmental 'anorexigens'.						●				-		1	B	A
1161	実験動物（反復投与毒性）	Christopher, B. and Marias, A.J.	28-Day oral toxicity study with FC-143 in albino mice, Final Report, Industrial Bio-Test Laboratories, Inc. Study No. 8532-10655	1977	3M Reference No. T-1742CoC, Lot 269. [cited in OECD (2008).]	No abstract available						●				企業データ		D	D
1162	実験動物（反復投与毒性）	Palazzolo, M.J.	Thirteen-week dietary toxicity study with T-5180, ammonium perfluorooctanoate (CAS No. 3825-26-1) in male rats. Final Report.	1993	Laboratory Project Identification HWI 6329-100. Hazleton Wisconsin, Inc. U.S. Environmental Protection Agency Administrative Record 226-0449. [cited in UK COT (2006); OECD (2008)].	No abstract available						●	●			企業データ		D	D
1163	実験動物（免疫毒性）	Singh TS, Lee S, Kim HH, Choi JK, Kim SH.	Perfluorooctanoic acid induces mast cell-mediated allergic inflammation by the release of histamine and inflammatory mediators	2012	Toxicol Lett. 2012 Apr 5;210(1):64-70. doi: 10.1016/j.toxlet.2012.01.014. Epub 2012 Feb 1.	Perfluorooctanoic acid (PFOA) has unique physical and chemical characteristics, water and oil repellency, thermal stability, and surfactant properties. PFOA has been regularly found in the blood of animals and humans worldwide, and has become an increasing concern because of its adverse effects in immune system. However, the role of PFOA in the allergic inflammation is not well-known. To further extend the immunotoxicity of PFOA, we examined the role of PFOA on the mast cell-mediated allergic inflammation and studied the possible mechanism of action. PFOA dose- and time-dependently increased histamine release from mast cells and serum histamine by the induction of intracellular calcium. PFOA exacerbated the IgE-dependent local allergic reaction in the mouse allergy model. PFOA induced gene expression of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and IL-8 in mast cells. The inducing effect of PFOA on the pro-inflammatory cytokines was nuclear factor-κB, p38 mitogen-activated protein kinase, and caspase-1 dependent. Furthermore, the activation of cyclooxygenase-2 by PFOA suggests the induction of allergic inflammatory mediators by the PFOA. Our findings provide evidence that PFOA, the known immunotoxic agent, induces mast cell-derived allergic inflammatory reactions by histamine release and expression of pro-inflammatory cytokines.						●				-		1	B	A
1164	実験動物（生殖発生毒性）	Abbott, B. D.; Wolf, C. J.; Schmid, J. E.; Das, K. P.; Zehr, R. D.; Helfant, L.; Nakayama, S.; Lindstrom, A. B.; Strynar, M. J.; Lau, C.	Perfluorooctanoic acid induced developmental toxicity in the mouse is dependent on expression of peroxisome proliferator activated receptor-alpha	2007	Toxicol Sci. 2007 Aug;98(2):571-81. doi: 10.1093/toxsci/kfm110. Epub 2007 May 7.	Perfluorooctanoic acid (PFOA) is a member of a family of perfluorinated chemicals that have a variety of applications. PFOA persists in the environment and is found in wildlife and humans. In mice, PFOA is developmentally toxic producing mortality, delayed eye opening, growth deficits, and altered pubertal maturation. PFOA activates peroxisome proliferators-activated receptor-alpha (PPARalpha), a pathway critical to the mode of induction of liver tumors in rodents. The present study uses 129S1/SvImJ wild-type (WT) and PPARalpha knockout (KO) mice to determine if PPARalpha mediates PFOA-induced developmental toxicity. Pregnant mice were dosed orally from gestation days 44578 with water or 0.1, 0.3, 0.6, 1, 3, 5, 10, or 20 mg PFOA/kg. PFOA did not affect maternal weight, embryonic implantation, number, or weight of pups at birth. At 5 mg/kg, the incidence of full litter resorptions increased in both WT and KO mice. In WT, but not KO, neonatal survival was reduced (0.6 mg/kg) and eye opening was delayed (1 mg/kg). There was a trend across dose for reduced pup weight (WT and KO) on several postnatal days (PND), but only WT exposed to 1 mg/kg were significantly different from control (PND7-10 and 22). Maternal factors (e.g., background genetics) did not contribute to differences in postnatal mortality, as PFOA induced postnatal mortality in heterozygous pups born to WT or KO dams. In conclusion, early pregnancy loss was independent of PPARalpha expression. Delayed eye opening and deficits in postnatal weight gain appeared to depend on PPARalpha expression, although other mechanisms may contribute. PPARalpha was required for PFOA-induced postnatal lethality and expression of one copy of the gene was sufficient to mediate this effect.	●	●	●	●		●			●	-		1	A	A
1165	実験動物（生殖発生毒性）	Albrecht, P. P.; Torsell, N. E.; Krishnan, P.; Ehresman, D. J.; Frame, S. R.; Chang, S. C.; Butenhoff, J. L.; Kennedy, G. L.; Gonzalez, F. J.; Peters, J. M.	A species difference in the peroxisome proliferator-activated receptor α-dependent response to the developmental effects of perfluorooctanoic acid	2013	Toxicol Sci. 2013 Feb;131(2):568-82. doi: 10.1093/toxsci/kfs318. Epub 2012 Nov 9.	This study examined the effect of prenatal perfluorooctanoic acid (PFOA) administration on pre- and postnatal development using peroxisome proliferator-activated receptor α (PPARα)-humanized mice to determine if species differences in receptor activity might influence the developmental effects induced by PFOA. Pregnant mice were treated daily with water or PFOA (3mg/kg) by po gavage from gestation day 1 (GD1) until GD17 and then either euthanized on GD18 or allowed to give birth and then euthanized on postnatal day 20 (PND20). No changes in average fetal weight, crown-to-rump length, or placental weight were observed on GD18. Expression of mRNA encoding the PPARα target genes acyl CoA oxidase (Acox1) and cytochrome P450 4a10 (Cyp4a10) in maternal and fetal liver was increased on GD18 in wild-type and PPARα-humanized mice but not in Pparα-null mice. On PND20, relative liver weight was higher in wild-type mice but not in Pparα-null mice or PPARα-humanized mice. Hepatic expression of Acox1 and Cyp4a10 mRNA was higher in wild-type mice but not in Pparα-null mice or PPARα-humanized mice on PND20. The percentage of mice surviving postnatally was lower in wild-type litters but not in litters from Pparα-null mice or PPARα-humanized mice. No changes in pup weight gain, onset of eye opening, or mammary gland development were found in any genotype. Results from these studies demonstrate that the developmental/postnatal effects resulting from prenatal PFOA exposure in mice are differentially mediated by mouse and human PPARα.	●		●	●		●			●	-			C	C
1166	実験動物（生殖発生毒性）	Argus Research Labs,	Support: Oral (stomach tube) developmental toxicity study of PFOS in rabbits with attachments and cover letter dated 0425000	2000	EPA/OTS; Doc #8EHQ-08000373	No abstract available	●	●								8EHQ-08000373で検索したが入手不可		D	D
1167	実験動物（生殖発生毒性）	Biegel, L. B.; Liu, R. C.; Hurtt, M. E.; Cook, J. C.	Effects of ammonium perfluorooctanoate on Leydig cell function: in vitro, in vivo, and ex vivo studies	1995	Toxicol Appl Pharmacol. 1995 Sep;134(1):18-25. doi: 10.1006/taap.1995.1164.	Ammonium perfluorooctanoate (C8) produced a dose-dependent increase in Leydig cell adenomas in Crl:CD BR (CD) rats fed 0, 30, or 300 ppm for 2 years. Administration of C8 to adult male CD rats, by gavage for 14 days, produced decreased serum and testicular interstitial fluid testosterone levels and increased serum estradiol levels. The C8-mediated decrease in the serum testosterone levels appeared to be due to a lesion at the level of the testis. These endocrine changes may play a role in the C8 induction of Leydig cell tumors. In the present work, C8 was examined for its ability to -1 directly affect Leydig cells in vitro using isolated Leydig cells from untreated rats and ex vivo using Leydig cells isolated from C8-treated rats, -2 affect testicular interstitial fluid hormone levels, and -3 induce aromatase activity. These studies were conducted to investigate the hypothesis that C8 produces an increase in estradiol by inducing cytochrome P450 XIX (aromatase), which converts testosterone to estradiol, and that the elevated estradiol levels ultimately produce Leydig cell hyperplasia and adenoma formation by acting as a mitogen or enhancing growth factor secretion. In the in vivo and ex vivo studies, adult male CD rats were gavaged with either 0 or 25 mg/kg/day C8 for 14 days. In addition to the ad libitum control, a second control group was pair-fed to the 25 mg/kg/day C8 group. In the in vitro and ex vivo studies, Leydig cells were isolated from testes of adult males by collagenase digestion followed by enrichment over Percoll gradients. A dose-dependent decrease in testosterone levels was observed in hCG-stimulated Leydig cells treated in vitro with C8 for 5 hr (IC50 approximately 200 microM). In contrast, ex vivo studies demonstrated an increase in testosterone production in hCG-stimulated Leydig cells from C8-treated rats when compared to Leydig cells isolated from either the ad libitum or pair-fed control rats. The in vitro data demonstrate that C8 directly inhibits testosterone release from Leydig cells, while the ex vivo data demonstrate that this inhibition is reversible.(ABSTRACT TRUNCATED AT 400 WORDS)	●	●		●						-			C	C
1168	実験動物（生殖発生毒性）	Birnbaum, L. S.; Fenton, S. E.	Cancer and developmental exposure to endocrine disruptors [Review]	2003	Environ Health Perspect 11: 389-394. doi: 10.1289/ehp.5686.	Developing organisms have increased susceptibility to cancer if they are exposed to environmental	●	●								-		D	D
1169	実験動物（生殖発生毒性）	Blake, B. E.; Cope, H. A.; Hall, S. M.; Keys, R. D.; Mahler, B. W.; Mccord, J.; Scott, B.; Stapleton, H. M.; Strynar, M. J.; Elmore, S. A.; Fenton, S. E.	Evaluation of Maternal, Embryo, and Placental Effects in CD-1 Mice following Gestational Exposure to Perfluorooctanoic Acid (PFOA) or Hexafluoropropylene Oxide Dimer Acid (HFPO-DA or GenX)	2020	Environ Health Perspect. 2020 Feb;128(2):27006. doi: 10.1289/EHP6233. Epub 2020 Feb 13.	BACKGROUND: Perfluorooctanoic acid (PFOA) is a poly- and perfluoroalkyl substance (PFAS) associated with adverse pregnancy outcomes in mice and humans, but little is known regarding one of its replacements, hexafluoropropylene oxide dimer acid (HFPO-DA, referred to here as GenX), both of which have been reported as contaminants in drinking water.OBJECTIVES: We compared the toxicity of PFOA and GenX in pregnant mice and their developing embryo-placenta units, with a specific focus on the placenta as a hypothesized target.METHODS: Pregnant CD-1 mice were exposed daily to PFOA (0, 1, or) or GenX (0, 2, or) via oral gavage from embryonic day (E) 1.5 to 11.5 or 17.5 to evaluate exposure effects on the dam and embryo-placenta unit. Gestational weight gain (GWG), maternal clinical chemistry, maternal liver histopathology, placental histopathology, embryo weight, placental weight, internal chemical dosimetry, and placental thyroid hormone levels were determined.RESULTS: Exposure to GenX or PFOA resulted in increased GWG, with increase in weight most prominent and of shortest latency with GenX exposure. Embryo weight was significantly lower after exposure to PFOA (9.4% decrease relative to controls). Effect sizes were similar for higher doses (PFOA and GenX) and lower doses (PFOA and GenX), including higher maternal liver weights, changes in liver histopathology, higher placental weights and embryo-placenta weight ratios, and greater incidence of placental abnormalities relative to controls. Histopathological features in placentas suggested that PFOA and GenX may exhibit divergent mechanisms of toxicity in the embryo-placenta unit, whereas PFOA- and GenX-exposed livers shared a similar constellation of adverse pathological features.CONCLUSIONS: Gestational exposure to GenX recapitulated many documented effects of PFOA in CD-1 mice, regardless of its much shorter reported half-life; however, adverse effects toward the placenta appear to have compound-specific signatures.	●	●								-			B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①クラン	文献クラン②クラン
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1170	実験動物（生殖発生毒性）	Butenhoff, J. L.; Ehresman, D. J.; Chang, S. C.; Parker, G. A.; Stump, D. G.	Gestational and lactational exposure to potassium perfluorooctanesulfonate (K+PFOS) in rats: developmental neurotoxicity	2009	Reprod Toxicol. 2009 Jun;27(3-4):319-330. doi: 10.1016/j.reprotox.2008.12.010. Epub 2008 Dec 31.	Perfluorooctanesulfonate (PFOS), a persistent and bioaccumulative compound, is widely distributed in humans and wildlife. Exposure of the human fetus and neonate to PFOS can occur in utero and via the mother's milk, respectively. Developmental studies have been conducted with PFOS in the past, including some developmental neurotoxicity endpoints. The objective of this study was to evaluate the functional and morphological changes to the nervous system in rats having gestational and lactational exposures to PFOS per current test guidelines (EPA OPPTS 870.63 and OECD 426). Female SD rats (25/dosage group) were given daily oral doses of either 0.0, 0.1, 0.3, or 1.0mg/kg-d potassium PFOS (K(+)PFOS) from gestation day (GD) 0 through postnatal day (PND) 20 Offspring were observed through PND 72 for growth, maturation, motor activity, learning and memory, acoustic startle reflex, various behavioral manifestations, and brain weight. Specimens were taken from dams, fetuses, and pups for serum and tissue PFOS concentration, thyroid status endpoints, and liver mRNA transcript analysis, and those results are reported in a companion article. No significant effect was noted on maternal health or reproductive outcomes from dosing of maternal rats with K(+)PFOS throughout gestation. Maternal body weights were statistically significantly lower in the 1.0mg/kg-d dosage group from PND 4 through the end of lactation. Offspring from K(+)PFOS-treated maternal groups did not differ significantly from controls with respect to birth weight, growth, age and weight at attainment of sexual maturation, learning and memory, acoustic startle, various behavioral endpoints, and brain weight. Male offspring from the 1.0mg/kg-d maternal treatment group displayed increased motor activity and reduced habituation on PND 17 but not on PND 13, 21, and 61 The maternal no-observed-adverse-effect-level (NOAEL) was 0.3mg/kg-d based on decreased body weights observed in lactation. The maternal dose associated with the NOAEL for male offspring was 0.3mg/kg-d based on increased motor activity and reduced habituation in the 1.0mg/kg-d maternal dose-group male offspring on PND 17 The maternal dose associated with the NOAEL for female offspring was >1.0mg/kg-d. Mean serum concentrations of PFOS reported in a companion article for the 0.3mg/kg-d group maternal rats are several hundred times higher than those reported for females in the United States general population.	●	●		●	●		●		●	-		1	B	A
1171	実験動物（生殖発生毒性）	Butenhoff, J. L.; Kennedy, G. L.; Frame, , S. R.; O'Connor, J. C.; York, R. G.	The reproductive toxicology of ammonium perfluorooctanoate (APFO) in the rat	2004	Toxicology. 2004 Mar 1;196(1-2):95-116. doi: 10.1016/j.tox.2003.11.005.	Ammonium perfluorooctanoate (APFO) is a surfactant used primarily as an aid in processing various fluoropolymers. Many toxicology and epidemiological studies have been conducted with APFO; however, no specific information regarding functional reproduction was previously available. Therefore, the potential reproductive toxicity of APFO across two generations of offspring was studied using current EPA OPPTS 870.38 guidelines. Male and female Sprague-Dawley rats were dosed orally with 0, 1, 3, 10, or 30 mg/kg APFO. Parental (P) generation rats (approximately 6 weeks old) were dosed at least 70 days prior to mating and until sacrificed (after mating for male rats; after weaning for female rats). F(1)-generation rats were dosed similarly, beginning at weaning. The F(2)-generation pups were maintained through 22 days of lactation. Reproductive parameters evaluated in P- and F(1)-generation rats included estrous cycling, sperm number and quality, mating, fertility, natural delivery, and litter viability and growth. Age at sexual maturation in F(1), anogenital distance in F(2), and presence of nipples (males) in F(2)-generation pups were also determined. Feed consumption, body-weight gain, selected organ-weights, gross pathology and appropriate histopathology were evaluated. Reproductive endpoints including mating, fertility, and natural delivery were not affected in either generation. P- and F(1)-generation male rats showed decreased body weight, and liver and kidney weight increases at all doses. The 30 mg/kg F(1)-generation pups had decreased birth weight. Viability was reduced in the 30 mg/kg F(1)-generation pups in apparent relationship to reduced body weight at birth and weaning; however, F(2)-generation pups at 30 mg/kg, although somewhat lighter, did not show a loss in viability. Preputial separation and vaginal opening were somewhat delayed at 30 mg/kg, but these rats went on to show normal reproductive performance. No-observed-adverse-effect-levels were >30 mg/kg for reproductive function of P- and F(1)-generation rats, 10 mg/kg for F(1)-generation pup mortality, birth weight, and sexual maturation, and less than 1mg/kg for male body-weight and organ-weight changes.	●	●		●		●	●		●	-			B	B
1172	実験動物（生殖発生毒性）	Chen, T.; Zhang, L.; Yue, J. Q.; Lv, Z. Q.; Xia, W.; Wan, Y. J.; Li, Y. Y.; Xu, S. Q.	Prenatal PFOS exposure induces oxidative stress and apoptosis in the lung of rat off-spring	2012	Reprod Toxicol. 2012 Jul;33(4):538-545. doi: 10.1016/j.reprotox.2011.03.003. Epub 2011 Mar 31.	Perfluorooctane sulfonate (PFOS) could induce neonatal pulmonary injuries in rodents. The aim of this study was to investigate the underlying mode of action. Pregnant rats were dosed orally with PFOS (0, 0.1 and 2.0mg/kgd) from gestation days (GD) 1 to 21 Lung samples from postnatal day (PND) 0 and 21 pups were analyzed for the toxic effects of PFOS. The results showed that maternal exposure to 2.0mg/kgd PFOS caused severe histopathological changes along with marked oxidative injuries and cell apoptosis in offspring lungs; at the same time, the ratio of Bax to Bcl-2, release of cytochrome c (Cyt c) from mitochondria to cytoplasm, expressions of Fas and Fas-L, and activities of caspase-3, -8 and -9 were up-regulated correspondingly. The results indicate that oxidative stress and both intrinsic and extrinsic cell death pathways were involved in prenatal PFOS exposure-induced injuries in postnatal lungs.	●	●		●	●				●	-			B	B
1173	実験動物（生殖発生毒性）	Chen, Y.; Zhou, L.; Xu, J.; Zhang, L.; Li, M.; Xie, X.; Xie, Y.; Luo, D.; Zhang, D.; Yu, X.; Yang, B.; Kuang, H.	Maternal exposure to perfluorooctanoic acid inhibits luteal function via oxidative stress and apoptosis in pregnant mice	2017	Reprod Toxicol. 2017 Apr;69:159-166. doi: 10.1016/j.reprotox.2017.02.010. Epub 2017 Feb 20.	Perfluorooctanoic acid (PFOA) is a synthetic perfluorinated compound, which has been reported to exert adverse effect on the pregnancy. However, whether it is associated with alteration of luteal function remains unknown. Mice were administered PFOA by gavage from gestational days (GD) 44568 or 13 PFOA treatment did not significantly affect numbers of embryo implantation. Nevertheless, on GD 13, 10mg/kg PFOA treatment significantly increased numbers of resorbed embryo. Furthermore, PFOA exposure markedly reduced serum progesterone levels but did not affect estradiol levels. Treatment also showed concomitant decreases in transcript levels for key steroidogenic enzymes, and reduced numbers and sizes of corpora lutea. In addition, PFOA administration inhibited activities of superoxide dismutase and catalase, and increased generation of hydrogen peroxide and malondialdehyde, and down-regulated level of Bcl-2 and up-regulated p53 and BAX proteins. In conclusion, PFOA exposure significantly inhibits luteal function via oxidative stress and apoptosis in pregnant mice.	●	●		●						-			B	B
1174	実験動物（生殖発生毒性）	Cheng, J.; Fujimura, M.; Zhao, W.; Wang, W.	Neurobehavioral effects, c-Fos/Jun expression and tissue distribution in rat offspring prenatally co-exposed to MeHg and PFOA: PFOA impairs Hg retention	2013	Chemosphere. 91: 758-764. doi: 10.1016/j.chemosphere.2013.02.016. Epub 2013 Mar 12.	Exposure to methylmercury (MeHg) and perfluorooctanoic acid (PFOA) can occur simultaneously as both contaminants are found in the same food sources, especially fish, seafood, marine mammals and milk. The aim of this study was to assess the effects of exposure to MeHg (10 μg mL(-1) in drinking water) and PFOA (10 μg mL(-1) in drinking water) from gestational day 1 to postnatal day (PND) 21, alone and in combination, on neurobehavioral development and the expression of c-Fos/Jun in different brain regions in the offspring. Our findings showed that exposure to MeHg alone, and exposure to MeHg combined with PFOA significantly induced cliff avoidance reflexes and negative geotaxis reflexes. And these effects appeared to be greater following exposure to MeHg alone. MeHg and/or PFOA exposure did not significantly impair motor coordination functions, or cause significant changes in c-Fos expression in the hippocampus and cerebellum, and spatial learning tests were similar to those in the controls, thus it was impossible to determine whether combined exposure to MeHg and PFOA had any additional effects on both hippocampus and cerebellum regions. However, a significant increase in the frequency of line crossing was observed in rats treated with MeHg or PFOA alone, and there were no significant differences between the MeHg+PFOA-treated group and the controls, suggesting that PFOA was antagonistic to MeHg toxicity in the locomotor activity test. Co-exposure to MeHg and PFOA decreased all tissue Hg concentrations in pups compared to the group exposed to MeHg only, suggesting that PFOA impaired Hg retention in different tissues.	●	●		●						-			C	C
1175	実験動物（生殖発生毒性）	Fenton, Suzanne E	Endocrine-disrupting compounds and mammary gland development: Early exposure and later life consequences [Review]	2006	Endocrinology. 2006 Jun;147(6 Suppl):S18-24. doi: 10.1210/en.2005-1131. Epub 2006 May 11.	Breast cancer is the most common non-skin cancer among women in this country. Breast cancer risk is significantly influenced by genetics, but over 70% of the women that are diagnosed have noninherited or sporadic cancer. The risk of breast cancer is thought to be modified by lifestyle and environment. Exposures to certain chemicals and hormone-mimicking or endocrine-disrupting compounds (EDCs) are suspected of contributing to increased breast cancer incidence as well as precocious puberty in the United States. Studies of EDC effects in rodents indicate that multiple toxicants can alter mammary gland development, with or without changing other markers of puberty. EDCs can cause transient and persistent effects on mammary gland development depending on dose, exposure parameters, and whether exposure was during critical periods of gland growth or differentiation. Adverse effects from these abnormal developmental patterns include the presence of carcinogen-sensitive structures in greater numbers or for longer periods in the gland and inhibited functional differentiation leading to malnutrition or increased mortality of their offspring. Developmental toxicants of the mammary gland could lead to an increase in the incidence of mammary tumors if they alter circulating or tissue-localized hormone levels, gland receptor expression patterns, hormone transport, or metabolism that results in altered response to endogenous hormones or growth factors. Environmental disruptors of rodent mammary gland development must be identified for informed decisions in epidemiological contributing to breast cancer risk, altered breast development during puberty, or inability to produce sufficient breast milk. studies aimed at identification of environmental factors	●	●								-			C	D
1176	実験動物（生殖発生毒性）	Filgo, Adam J; Quist, Erin M; Hoenerhoff, Mark J; Brix, Amy E; Kissling, Grace E; Fenton, Suzanne E	Perfluorooctanoic acid (PFOA)-induced liver lesions in two strains of mice following developmental exposures: PPARalpha is not required	2015	Toxicol Pathol. 2015 Jun;43(4):558-68. doi: 10.1177/0192623314558463. Epub 2014 Nov 14.	Perfluorooctanoic acid (PFOA) is a ubiquitous pollutant that causes liver toxicity in rodents, a process believed to be dependent on peroxisome proliferator-activated receptor-alpha (PPARα) activation. Differences between humans and rodents have made the human relevance of some health effects caused by PFOA controversial. We analyzed liver toxicity at 18 months following gestational PFOA exposure in CD-1 and 129/Sv strains of mice and compared PFOA-induced effects between strains and in wild type (WT) and PPARα-knockout (KO) 129/Sv mice. Pregnant mice were exposed daily to doses (0.01-5 mg/kg/BW) of PFOA from gestation days 1 to 17. The female offspring were necropsied at 18 months, and liver sections underwent a full pathology review. Hepatocellular adenomas formed in PFOA-exposed PPARα-KO 129/Sv and CD-1 mice and were absent in untreated controls from those groups and WT 129/Sv. Hepatocellular hypertrophy was significantly increased by PFOA exposure in CD-1, and an increased severity was found in WT 129/Sv mice. PFOA significantly increased nonneoplastic liver lesions in PPARα-KO mice (hepatocyte hypertrophy, bile duct hyperplasia, and hematopoietic cell proliferation). Low-dose gestational exposures to PFOA induced latent PPARα-independent liver toxicity that was observed in aged mice. Evidence of liver toxicity in PPARα-KO mice warrants further investigation into PPARα-independent pathways.	●	●	●	●		●			●	-			C	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1177	実験動物（生殖発生毒性）	Fuentes, S.; Colomina, M. T.; Vicens, P.; Franco-Pons, N.; Domingo, J. L.	Concurrent exposure to perfluorooctane sulfonate and restraint stress during pregnancy in mice: effects on postnatal development and behavior of the offspring	2007	Toxicol Sci. 2007 Aug;98(2):589-98. doi: 10.1093/toxsci/kfm121. Epub 2007 May 15.	The combined effects of maternal restraint stress and perfluorooctane sulfonate (PFOS) on postnatal development and behavior of the offspring were assessed in mice. Thirty-four plug positive females were randomly divided into two groups. Animals were given by gavage 0 and 6 mg PFOS/kg/day on gestation days 12-18. One-half of the animals in each group was subjected to restraint stress (30 min per session, three sessions per day) during the same period. Neither restraint nor PFOS exposure significantly modified maternal food or water consumption. Pups of dams exposed to 6 mg/kg of PFOS showed a reduced body weight on postnatal days 4 and 8 Moreover, PFOS exposure induced some delay in developmental landmarks and neuromotor maturation. Maternal restraint stress reduced activity in an open-field when combined with 6 mg PFOS/kg/day. In addition, in males prenatal restraint stress impaired motor coordination in a rotarod. The current results indicate that concurrent exposure to PFOS and restraint stress during pregnancy induces opposite effects on developmental parameters in the pups. These effects consist in a general delayed maturation trend induced by PFOS exposure, and a general accelerated maturation pattern induced by prenatal stress. Interactive effects between PFOS and maternal stress were observed in young adult mice. These effects consisted mainly in a diminished activity in an open-field test.	●	●		●	●					-		B	B
1178	実験動物（生殖発生毒性）	Goulding, D. R.; White, S. S.; Mcbride, S. J.; Fenton, S. E.; Harry, G. J.	Gestational exposure to perfluorooctanoic acid (PFOA): Alterations in motor related behaviors	2017	Neurotoxicology. 58: 110-119. doi: 10.1016/j.neuro.2016.11.008. Epub 2016 Nov 22.	Perfluoroalkyl and polyfluoroalkyl substances are used in commercial applications and developmental exposure has been implicated in alterations in neurobehavioral functioning. While associations between developmental perfluorooctanoic acid (PFOA) exposure and human outcomes have been inconsistent, studies in experimental animals suggest alterations in motor related behaviors. To examine a dose-response pattern of neurobehavioral effects following gestational exposure to PFOA, pregnant CD-1 mice received PFOA (0, 0.1, 0.3, 1.0mg/kg/day) via oral gavage from gestational day 44578 and the male offspring examined. Motor activity assessments on postnatal day (PND)18, 19, and 20 indicated a shift in the developmental pattern with an elevated activity level observed in the 1.0mg/kg/day dose group on PND18. In the adult, no alterations were observed in body weights, activity levels, diurnal pattern of running wheel activity, startle response, or pre-pulse startle inhibition. In response to a subcutaneous injection of saline or nicotine (80μg/kg), all animals displayed a transient increase in activity likely associated with handling with no differences observed across dose groups. Inhibition of motor activity over 18days of 400μg/kg nicotine injection was not significantly different across dose groups. Hyperactivity induced by 2mg/kg (+)-methamphetamine hydrochloride intraperitoneal injection was significantly lower in the 1.0mg/kg/day PFOA dose group as compared to controls. Taken together, these data suggest that the effects on motor-related behaviors with gestational PFOA exposure do not mimic those reported for acute postnatal exposure. Changes were not observed at dose levels under 1.0mg/kg/day PFOA. Further examination of pathways associated with methamphetamine-induced activity is warranted.	●	●		●						-		C	C
1179	実験動物（生殖発生毒性）	Grasty, R. C.; Bjork, J. A.; Wallace, K. B.; Lau, C. S.; Rogers, J. M.	Effects of prenatal perfluorooctane sulfonate (PFOS) exposure on lung maturation in the perinatal rat	2003	Birth Defects Res B Dev Reprod Toxicol. 68: 465-471. doi: 10.1002/bdrb.20059	BACKGROUND: Perfluorooctane sulfonate (PFOS), found widely in wildlife and humans, is environmentally and metabolically stable. Environmental PFOS may be from its use as a surfactant, hydrolysis of perfluorooctanesulfonyl fluoride, and degradation of N‐alkyl‐perfluorooctanesulfonamide compounds formerly used in numerous applications. Prenatal exposure to PFOS in rodents causes neonatal mortality; treatment on gestation days (GD) 19–20 is sufficient to induce neonatal death in rats. Affected pups are born alive but present with labored breathing. Their lungs are pale and often do not expand fully on perfusion. METHODS: Pregnant Sprague–Dawley rats received 0, 25, or 50 mg/kg/day PFOS/K+ orally on GD 19‐20. Lungs from GD 21 fetuses and neonates were prepared for histology and morphometry. Rescue experiments included co‐administration of dexamethasone or retinyl palmitate with PFOS. Pulmonary surfactant was investigated with mass spectrometry in GD 21 amniotic fluid and neonatal lungs. Microarray analysis was carried out on PND 0 lungs. RESULTS: Histologically, alveolar walls were thicker in lungs of PFOS‐exposed newborns compared to controls. The ratio of solid tissue:small airway was increased, suggesting immaturity. Rescue studies were ineffective. Phospholipid concentrations and molecular speciation were unaffected by PFOS. No changes in markers of alveolar differentiation were detected by microarray analysis. CONCLUSIONS: Morphometric changes in lungs of PFOS exposed neonates were suggestive of immaturity, but the failure of rescue agents and normal pulmonary surfactant profile indicate that the labored respiration and mortality observed in PFOS‐treated neonates was not due to lung immaturity.	●	●		●	●				●	-	1	A	A
1180	実験動物（生殖発生毒性）	Grasty, R. C.; Wolf, D. C.; Grey, B. E.; Lau, C. S.; Rogers, J. M.	Prenatal window of susceptibility to perfluorooctane sulfonate-induced neonatal mortality in the Sprague-Dawley rat	2003	Birth Defects Res B Dev Reprod Toxicol. 2003 Dec;68(6):465-71. doi: 10.1002/bdrb.10046.	The critical period for increased neonatal mortality induced by perfluorooctane sulfonate (PFOS) exposure was evaluated in the rat. Timed-pregnant Sprague-Dawley rats were treated by oral gavage with 25 mg/kg/d PFOS/K(+) on four consecutive days (gestation days (GD) 2-5, 6-9, 10-13, 14-17, or 17-20) or with 0, 25, or 50 mg/kg/d PFOS/K(+) on GD 19-20. Controls received vehicle (10 ml/kg 0.005 Tween-20) on these days. Maternal weight gain was reduced in treated animals during dosing, as were food and water consumption. Following a 4-day treatment, litter size at birth was unaffected while pup weight was similarly reduced in the three earliest PFOS groups. All PFOS groups experienced decreases in survival while controls remained near 100%. Neonatal survival decreased in groups dosed later during gestation, approaching 1 with dosing on GD 17-20. Most deaths occurred before postnatal day (PND) 4, with the majority in the first 24 hours. Maternal serum PFOS levels on GD 21 were higher in groups exhibiting higher mortality. Following a 2-day treatment, PFOS groups experienced significant pup mortality by PND 1 Neonatal mortality continued through PND 5, when survival was 98, 66, and 0.03 for the 0, 25, and 50 mg/kg groups, respectively. Pup weight was reduced in treated groups with surviving litters. Gross dissection and histological examination of lungs revealed differences in maturation between control and treated animals on PND 0 We conclude that exposure to PFOS late in gestation is sufficient to induce 1 pup mortality and that inhibition of lung maturation may be involved.	●	●		●					●	-	1	A	A
1181	実験動物（生殖発生毒性）	Hines, E. P.; White, S. S.; Stanko, J. P.; Flournoy, E. A. G.; Lau, C.; Fenton, S. E.	Phenotypic dichotomy following developmental exposure to perfluorooctanoic acid (PFOA) in female CD-1 mice: low doses induce elevated serum leptin and insulin, and overweight in mid-life	2009	Mol Cell Endocrinol. 304: 97-105. doi: 10.1016/j.mce.2009.02.021. Epub 2009 Mar 9.	The synthetic surfactant, perfluorooctanoic acid (PFOA) is a proven developmental toxicant in mice, causing pregnancy loss, increased neonatal mortality, delayed eye opening, and abnormal mammary gland	●	●	●	●		●				-		D	C
1182	実験動物（生殖発生毒性）	Ishida, K.; Tsuyama, Y.; Sanoh, S.; Ohta, S.; Kotake, Y.	Perfluorooctane sulfonate induces neuronal vulnerability by decreasing GluR2 expression	2017	Arch Toxicol. 91: 885-895. doi: 10.1007/s00204-016-1731-x. Epub 2016 May 7.	Perfluorooctane sulfonate (PFOS) is a persistent environmental contaminant. Although studies have described PFOS-induced neurotoxicity in animal brains and neuronal cells, the molecular mechanisms of PFOS-induced neurotoxicity based on the distribution properties, especially during developmental periods, have not been clarified. To clarify the mechanisms of PFOS-induced neuronal vulnerability during developmental periods, we examined changes in glutamate receptor 2 (GluR2) expression and related neurotoxicity in PFOS-treated primary cortical neurons and neonatal rat brains. Exposure of cortical neurons to 1 μM PFOS for 9 days resulted in decreased α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunit GluR2 expression, which subsequently enhanced vulnerability to glutamate by increasing intracellular Ca(2+) concentrations. The brain-plasma ratio of PFOS in pups was approximately five times higher than that in dams, although there were no differences in liver-plasma ratio between dams and pups. GluR2 expression in pup cerebral cortex decreased after exposure to 2.0 mg/kg PFOS, and kainic acid induced histopathological abnormalities in PFOS-exposed pups. Our findings suggest that decreased neuronal GluR2 expression is involved in PFOS-induced neurotoxicity, especially during the fetal and neonatal periods.	●	●								-		C	C
1183	実験動物（生殖発生毒性）	Jiang, W.; Deng, Y.; Song, Z.; Xie, Y.; Gong, L.; Chen, Y.; Kuang, H.	Gestational Perfluorooctanoic Acid Exposure Inhibits Placental Development by Dysregulation of Labyrinth Vessels and uNK Cells and Apoptosis in Mice	2020	Front Physiol. 11: 51. doi: 10.3389/fphys.2020.00051. eCollection 2020.	Perfluorooctanoic acid (PFOA) is a widely used perfluorinated compound and known to cause developmental toxicity which includes the increase of resorbed embryo, decrease of fetal survival, and fetal growth retardation. Nevertheless, whether it is associated with alteration of placental development remains unknown. Pregnant mice were gavaged with 0, 2.5, 5, 10 mg PFOA /kg/day from pregnancy day (PD) 1 to PD 13 Results showed that PFOA exposure markedly decreased the placental weight and caused interstitial edema of placenta. Laminin staining indicated that blood sinusoids area was shrunken in placenta of PFOA-exposed mice. Furthermore, PFOA treatment significantly reduced numbers of uNK cells. Western blot analysis revealed that levels of Bax and cleaved-caspase 3 proteins were markedly up-regulated in PFOA-treated groups. In addition, TEM examination showed that PFOA treatment caused rupture of nuclear membrane and nuclear pyknosis and fragmentation. Thus, our results suggested that gestational PFOA exposure significantly inhibited development of early placenta through shrinkage of labyrinth vessels and downregulation of uNK cells and apoptosis induction, which may result in adverse gestational outcomes.	●	●								-		B	B
1184	実験動物（生殖発生毒性）	Johansson, Niclas; Eriksson, Per; Viberg, Henrik	Neonatal exposure to PFOS and PFOA in mice results in changes in proteins which are important for neuronal growth and synaptogenesis in the developing brain	2009	Toxicol Sci. 2009 Apr;108(2):412-8. doi: 10.1093/toxsci/kfp029. Epub 2009 Feb 11.	Perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) belong to the family of perfluorinated compounds. They are used in industrial and consumer applications, e.g., clothing fabrics, carpets, and food packaging. PFOS and PFOA are present in the environment and are found in dust and human milk, which implies that newborns and toddlers can be directly exposed to these agents during brain development. Recently, we reported that PFOS and PFOA can cause neurobehavioral defects and changes in the cholinergic system, in the adult animal, when given directly to neonatal mice, and thereby showing similarities with other investigated persistent organic pollutants, such as dichloro-diphenyl-trichloroethan, polychlorinated biphenyls, and polybrominated diphenyl ethers (PBDEs). In recent studies, we have also seen that highly brominated PBDEs can affect the levels of proteins that are important for neuronal growth and synaptogenesis in the neonatal mouse brain. The present study shows that a single oral dose of either 21 micromol PFOS or PFOA/kg body weight (11.3 or 8.70 mg), given directly to the neonatal mice on postnatal day 10, significantly increased the levels of CaMKII, GAP-43, and synaptophysin in the hippocampus of the neonatal mouse. Both compounds significantly increased the levels of synaptophysin and tau in cerebral cortex, and PFOA also increased the levels of tau in hippocampus. These proteins are important for normal brain development, and altered levels of these proteins during a critical period of the brain growth spurts could be one of the mechanisms behavioral defects. behind earlier reported	●	●		●	●	●			●	-		C	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献クラン①C	文献クラン②C
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1185	実験動物（生殖発生毒性）	Johansson, N.; Fredriksson, A.; Eriksson, P.	Neonatal exposure to perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) causes neurobehavioural defects in adult mice	2008	Neurotoxicology. 2008 Jan;29(1):160-9. doi: 10.1016/j.neuro.2007.10.008. Epub 2007 Nov 1.	Perfluorinated compounds (PFCs) are found in applications such oil/water repellents for clothing fabrics, carpets, food packaging, lubricants, surfactants and fire extinguishers. PFCs are persistent in the environment. They have been found in humans and in wildlife. We reported earlier that persistent organic pollutants (POPs), such as DDT, PCBs and BFRs, caused developmental neurotoxic defects in mice, manifested as persistent aberrations in spontaneous behaviour, habituation capability, learning and memory, and changes in the cholinergic system in adults, when mice were exposed during a critical period of neonatal brain development. The present study was conducted to see whether PFCs can cause similar developmental neurotoxic effects as earlier observed for POPs as PCBs and PBDEs. NMRI male mice were exposed to a single-oral dose, either 1.4 or 21 micromol/kg body weight of PFOS (0.75 or 11.3 mg), PFOA (0.58 or 8.7 mg), or PFDA (0.72 or 10.8 mg), via a metal gastric-tube at the age of 10 days. The control animals received in the same manner 10 ml/kg body weight of the 0.2 fat emulsion vehicle. Spontaneous behaviour (locomotion, rearing, and total activity), and habituation were observed in 2- and 4-month-old mice. The susceptibility of the cholinergic system was explored in a nicotine-induced spontaneous behaviour test in 4-month-old mice. Deranged spontaneous behaviour was observed in mice exposed to PFOS and PFOA, manifested as reduced and/or lack of habituation and hyperactivity in adult mice. These effects were also seen to worse with age. Neonatal exposure to PFOS and PFOA affected the cholinergic system, manifested as a hypoactive response to nicotine, compared to a hyperactive response to nicotine in controls. These developmental neurotoxic effects are similar to those we reported earlier for PCBs and PBDEs. This suggests that PFOS and PFOA be included in the group of POPs known to be developmental neurotoxicants.	●	●	●	●	●	●			●	-		C	C
1186	実験動物（生殖発生毒性）	Keil, D. E.; Mehlmann, T.; Butterworth, L.; Peden-Adams, M. M.	Gestational exposure to perfluorooctane sulfonate suppresses immune function in B6C3F1 mice	2008	Toxicol Sci. 103: 77-85. doi: 10.1093/toxsci/kfn015. Epub 2008 Feb 5.	Perfluorinated alkyl acids (PFAAs) are used in a multitude of applications and are categorized as high-production volume chemicals produced in quantities exceeding 10000 lbs/year. As a result, widespread exposure has been documented in adults, children, and infants. It is generally accepted that children are more sensitive to the effects of xenobiotic exposures during fetal and postnatal periods of development; therefore, considerable efforts are required to investigate the potential impact of a model PFAA, perfluorooctane sulfonate (PFOS) on children's immunological health. Using the pairing of female C57BL/6N mice with male C3H/HeJ, developmental immunotoxicity was evaluated in B6C3F1 pups following oral maternal exposure to PFOS on gestations days 1-17. Exposure levels included 0.1, 1, and 5 mg/kg/day PFOS. Natural killer (NK) cell activity, SRBC IgM plaque assay, CD4/8 lymphocytic subpopulations, nitrite production in peritoneal macrophages, and body/organ weights were evaluated at 4 and 8 weeks of age in F1 pups. No significant dose-responsive changes in maternal or pup body weights, flow cytometry, or macrophage function were observed, yet hepatomegaly was indicated in F1 male pups at 4 weeks of age. Functional deficits were not evident until 8 weeks of age when NK cell function and IgM production were significantly decreased. When compared with females, male pups were more sensitive to the effects of PFOS thereby establishing a no observed adverse effect level and low observed adverse effect level of 0.1 and 1 mg/kg/day (males only) following maternal PFOS exposure level, respectively. This study establishes that the developing immune system is sensitive to the effects of PFOS and results in functional deficits in innate and humoral immunity detectable at adulthood.	●	●	●	●	●				●	-		B	B
1187	実験動物（生殖発生毒性）	Lai, K. P.; Lee, J. C.; Wan, H. T.; Li, J. W.; Wong, A. Y.; Chan, T. F.; Oger, C.; Galano, J. M.; Durand, T.; Leung, K. S.; Leung, C. C.; Li, R.; Wong, C. K.	Effects of in Utero PFOS Exposure on Transcriptome, Lipidome, and Function of Mouse Testis	2017	Environ Sci. Technol 51: 8782-8794. doi: 10.1021/acs.est.7b02102. Epub 2017 Jul 12.	Transcriptomic and LC-MS/MS-based targeted lipidomic analyses were conducted to identify the effects of in utero PFOS exposure on neonatal testes and its relation to testicular dysfunction in adult offspring. Pregnant mice were orally administered 0.3 and 3 μg PFOS/g body weight until term. Neonatal testes (P1) were collected for the detection of PFOS, and were subjected to omics study. Integrated pathway analyses using DAVID, KEGG, and IPA underlined the effects of PFOS exposure on lipid metabolism, oxidative stress and cell junction signaling in testes. LC-MS/MS analysis showed that the levels of adrenic acid and docosahexaenoic acid (DHA) in testes were significantly reduced in the PFOS treatment groups. A significant linear decreasing trend in eicosapentaenoic acid and DHA with PFOS concentrations was observed. Moreover, LOX-mediated 5-hydroxyeicosatetraenoic acids (HETE) and 15-HETE from arachidonic acid in the testes were significantly elevated and a linear increasing trend of 15-HETE concentrations was detected with doses of PFOS. The perturbations of lipid mediators suggested that PFOS has potential negative impacts on testicular functions. Postnatal analysis of male offspring at P63 showed significant reductions in serum testosterone and epididymal sperm count. This study sheds light into the as yet unrevealed action of PFOS on lipid mediators in affecting testicular functions.	●	●								-		B	B
1188	実験動物（生殖発生毒性）	Lau, Christopher; Thibodeaux, Julie R; Hanson, Roger G; Narotsky, Michael G; Rogers, John M; Lindstrom, Andrew B; Strynar, Mark J	Effects of perfluorooctanoic acid exposure during pregnancy in the mouse	2006	Toxicol Sci. 2006 Apr;90(2):510-8. doi: 10.1093/toxsci/kfj105. Epub 2006 Jan 16.	Perfluorooctanoic acid (PFOA), a member of the perfluoroalkyl acids that have wide commercial applications, has recently been detected in humans and wildlife. The current study characterizes the developmental toxicity of PFOA in the mouse. Timed-pregnant CD-1 mice were given 1, 3, 5, 10, 20, or 40 mg/kg PFOA by oral gavage daily from gestational day (GD) 1 to 17; controls received an equivalent volume (10 ml/kg) of water. PFOA treatment produced dose-dependent full-litter resorptions; all dams in the 40-mg/kg group resorbed their litters. Weight gain in dams that carried pregnancy to term was significantly lower in the 20-mg/kg group. At GD 18, some dams were sacrificed for maternal and fetal examinations (group A), and the rest were treated once more with PFOA and allowed to give birth (group B). Postnatal survival, growth, and development of the offspring were monitored. PFOA induced enlarged liver in group A dams at all dosages, but did not alter the number of implantations. The percent of live fetuses was lower only in the 20-mg/kg group (74 vs. 94% in controls), and fetal weight was also significantly lower in this group. However, no significant increase in malformations was noted in any treatment group. The incidence of live birth in group B mice was significantly lowered by PFOA: ca. 70% for the 10- and 20-mg/kg groups compared to 96% for controls. Postnatal survival was severely compromised at 10 or 20 mg/kg, and moderately so at 5 mg/kg. Dose-dependent growth deficits were detected in all PFOA-treated litters except the 1-mg/kg group. Significant delays in eye-opening (up to 2-3 days) were noted at 5 mg/kg and higher dosages. Accelerated sexual maturation was observed in male offspring, but not in females. These data indicate maternal and developmental toxicity of PFOA in the mouse, leading to early pregnancy loss, compromised postnatal survival, delays in general growth and development, and sex-specific alterations in pubertal maturation.	●	●	●	●		●	●		●	-		1	A	A
1189	実験動物（生殖発生毒性）	Lau, C.; Thibodeaux, J. R.; Hanson, R. G.; Rogers, J. M.; Grey, B. E.; Stanton, M. E.; Butenhoff, J. L.; Stevenson, L. A.	Exposure to perfluorooctane sulfonate during pregnancy in rat and mouse	2003	Toxicol Sci. 2003 Aug;74(2):382-92. doi: 10.1093/toxsci/kfg122. Epub 2003 May 28.	The postnatal effects of in utero exposure to perfluorooctane sulfonate (PFOS, C8F17SO3-) were evaluated in the rat and mouse. Pregnant Sprague-Dawley rats were given 1, 2, 3, 5, or 10 mg/kg PFOS daily by gavage from gestation day (GD) 2 to GD 21; pregnant CD-1 mice were treated with 1, 5, 10, 15, and 20 mg/kg PFOS from GD 1 to GD 18 Controls received 0.005 Tween-20 vehicle (1 ml/kg for rats and 10 ml/kg for mice). At parturition, newborns were observed for clinical signs and survival. All animals were born alive and initially appeared to be active. In the highest dosage groups (10 mg/kg for rat and 20 mg/kg for mouse), the neonates became pale, inactive, and moribund within 30-60 min, and all died soon afterward. In the 5 mg/kg (rat) and 15 mg/kg (mouse) dosage groups, the neonates also became moribund but survived for a longer period of time (8-12 h). Over 0.95 of these animals died within 24 h. Approximately 0.5 of offspring died at 3 mg/kg for rat and 10 mg/kg for mouse. Cross-fostering the PFOS-exposed rat neonates (5 mg/kg) to control nursing dams failed to improve survival. Serum concentrations of PFOS in newborn rats mirrored the maternal administered dosage and were similar to those in the maternal circulation at GD 21; PFOS levels in the surviving neonates declined in the ensuing days. Small but significant and persistent growth lags were detected in surviving rat and mouse pups exposed to PFOS prenatally, and slight delays in eye opening were noted. Significant increases in liver weight were observed in the PFOS-exposed mouse pups. Serum thyroxine levels were suppressed in the PFOS-treated rat pups, although triiodothyronine and thyroid-stimulating hormone [TSH] levels were not altered. Choline acetyltransferase activity (an enzyme that is sensitive to thyroid status) in the prefrontal cortex of rat pups exposed to PFOS prenatally was slightly reduced, but activity in the hippocampus was not affected. Development of learning, determined by T-maze delayed alternation in weanling rats, was not affected by PFOS exposure. These results indicate that in utero exposure to PFOS severely compromised postnatal survival of neonatal rats and mice, and caused delays in growth and development that were accompanied by hypothyroxinemia in the surviving rat pups.	●	●	●	●	●		●		●	-		1	A	A
1190	実験動物（生殖発生毒性）	Lee, C. K.; Kang, S. G.; Lee, J. T.; Lee, S. W.; Kim, J. H.; Kim, D. H.; Son, B. C.; Kim, K. H.; Suh, C. H.; Kim, S. Y.; Park, Y. B.	Effects of perfluorooctane sulfuric acid on placental PRL-family hormone production and fetal growth retardation in mice	2015	Mol Cell Endocrinol. 401: 165-172. doi: 10.1016/j.mce.2014.10.026. Epub 2014 Nov 6.	Perfluorooctane sulfuric acid (PFOS) is a persistent organic pollutant, causes fetal growth retardation but the mechanism is still unclear. This study focused on PFOS-induced toxicity such as placental trophoblast cell histopathological changes, endocrine function (i.e., prolactin (PRL)-family hormone production) and subsequent fetal growth retardation in mice. Maternal body weight gain, placental and fetal weights were significantly decreased in proportion to PFOS dosage. Placental efficiency (fetal weight/placental weight) was significantly reduced dose-dependently. Necrotic changes were observed in PFOS-treated placental tissues, and the area of injury increased dose-dependently. Finally, mRNA levels and maternal serum concentrations of the PRL-family hormones (mPL-II, mPLP-Cα, mPLP-K) were significantly reduced dose-dependently. In addition, the changing pattern between PRL-family hormone concentrations and fetal body weight was positively correlated. These results suggest that gestational PFOS treatment induces placental histopathological changes and disruption of endocrine function, finally may lead to fetal growth retardation in mice.	●	●	●	●					●	-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1191	ヒト（生殖発生毒性）	Lee, Y. J.; Kim, M. K.; Bae, J.; Yang, J. H.	Concentrations of perfluoroalkyl compounds in maternal and umbilical cord sera and birth outcomes in Korea	2013	Chemosphere. 2013 Feb;90(5):1603-9. doi: 10.1016/j.chemosphere.2012.08.035. Epub 2012 Sep 16.	This study analyzed the concentrations of perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA) and perfluorohexane sulfonate (PFHxS) in maternal and umbilical cord sera at delivery from the general population in Korea. Seventy samples were analyzed with ion-pairing and LC/MS/MS. PFOS, PFOA and PFHxS were detected in both maternal and umbilical cord sera. There was a high correlation of PFC concentrations between maternal and cord serum samples, implying transplacental transport. Ranking of transplacental transfer efficiency was PFOA>PFHxS>PFOS. Student's t-tests revealed that concentrations of maternal PFOA were related with decreases in birth weight, birth length and ponderal index, suggesting a possible impact on fetal growth. With multiple logistic regression models, maternal PFOS concentration showed a significant inverse association with ponderal index (OR=0.22; 0.95 CI, 0.05-0.90). Umbilical cord PFHxS concentration showed a significant inverse association with birth weight (OR=0.26; 0.95 CI, 0.08-0.85) or a marginally significant inverse association with birth length (OR=0.33; 0.95 CI, 0.09-1.17). This is the first report demonstrating an inverse association of birth outcomes with PFHxS exposure. Concentrations of maternal PFOA were decreased with parity, implying that delivery is one of the major routes for PFOA elimination in women. This study demonstrated prenatal exposure of PFCs through placental transfer which could result in possible developmental effects in the population sampled. Our results may provide data basis to conduct a larger scale investigation into developmental effects of PFCs in the future and contribute to understanding levels of PFC contaminations from a variety of populations in the globe.	●	●	●	●			●		●	-		B	-
1192	実験動物（生殖発生毒性）	Li, D.; Song, P.; Liu, L.; Wang, X.	Perfluorooctanoic acid exposure during pregnancy alters the apoptosis of uterine cells in pregnant mice	2018	Int J Clin Exp Pathol. 11: 5602-5611.eCollection 2018.	The present study investigates the effects of perfluorooctanoic acid (PFOA) exposure on reproductive toxicity and uterine apoptosis in pregnant mice. Sixty pregnant mice were randomly divided into 6 groups (groups A, B, C, D, E and F). In control group (A), the mice received distilled water at 10 mg/kg body weight per day on gestation days (GD) 1 to 17 The mice in group B, C, D, E and F were treated with PFOA solution at 1, 5, 10, 20 and 40 mg/kg body weight respectively from GD1 to GD17. The mice were sacrificed on GD18. The distribution and expression of Fas, FasL, Bcl-2, Bax, and Caspase-3 in uterine cells were detected by immunohistochemistry. The apoptosis of uterine cells was detected by TdT-mediated dUTP Nick-End Labeling (TUNEL). Results showed that the expression of Fas, FasL, and Caspase 3 in uterus increased significantly after PFOA was applied. The expression of Bcl-2 was decreased significantly and the expression of Bax was increased significantly. The ratio of Bcl-2/Bax decreased significantly compared with the control group (P<0.01). PFOA exposure increased the number of apoptotic uterine cells in a dose-dependent manner. The results indicated that PFOA could accelerate the apoptosis of uterine cells, and lead to slow embryo development or abortion by regulating the expression of Fas, FasL, Bax, Bcl-2 and Caspase-3 in uterine cells.	●	●	●							-		C	C
1193	実験動物（生殖発生毒性）	Li, D.; Zhang, L.; Zhang, Y.; Guan, S.; Gong, X.; Wang, X.	Maternal exposure to perfluorooctanoic acid (PFOA) causes liver toxicity through PPAR-α pathway and lowered histone acetylation in female offspring mice	2019	Environ Sci Pollut Res Int. 26: 18866-18875. doi: 10.1007/s11356-019-05258-z. Epub 2019 May 7.	The study was conducted to investigate the liver toxicity in female offspring mice induced by maternal exposure to perfluorooctanoic acid (PFOA). Fifty pregnant Kunming mice were randomly divided into 5 groups with 10 of each, which were treated with 0.2 mL PFOA solution dissolved with deionized water at 0, 1, 2.5, 5, and 10 mg/kg BW, respectively, from the pregnancy day (PND) 0 to day 17 Female offspring mice were sacrificed to collect serum and liver at postpartum day 21 The results showed that PFOA significantly reduced the body weight at weaning and the survival rate of the female offspring mice ($P < 0.01$) increased the liver index of the pups ($P < 0.01$). Meanwhile, PFOA also caused hepatic bleeding, local necrosis, and enlargement of hepatocytes and vacuolization. The levels of serum AST, ALT, SOD, and CAT in PFOA treatment group were upregulated significantly ($P < 0.01$). The expressions of Acot1, Acox1, and Acsl1 genes were increased significantly ($P < 0.01$). The expression of PPAR-α gene was decreased significantly ($P < 0.01$). There was no significant difference in the expression of Cpt1a gene among the 5 groups. HAT activity was reduced significantly and HDAC activity was increased significantly. The expression of anti-acetyl-histone H3 and acetyl-histone H4 was reduced significantly. Thus, our findings indicate that exposure to PFOA during pregnancy affects the growth and development of the pups and causes liver damage, disrupting the secretion of enzymes involved in fatty acid oxidation induced by PPAR-α, leading to liver oxidative stress and a decrease in the degree of histone acetylation. Elevated HDAC may aggravate downstream fatty acid metabolism disorders through PPAR-α.	●	●	●							-		C	B
1194	実験動物（生殖発生毒性）	Li, X.; Ye, L.; Ge, Y.; Yuan, K.; Zhang, Y.; Liang, Y.; Wei, J.; Zhao, C.; Lian, Q. Q.; Zhu, X.; Ge, R. S.	In utero perfluorooctane sulfonate exposure causes low body weights of fetal rats: A mechanism study	2016	Placenta. 39: 125-133. doi: 10.1016/j.placenta.2016.01.010. Epub 2016 Jan 22.	OBJECTIVES: The objective of the present study is to investigate the mechanism of perfluorooctane sulfonate-induced low body weight of fetus by analysis of glucocorticoid metabolizing enzyme 11β-hydroxysteroid dehydrogenase 2 and gene expression profiling of the placenta after in utero PFOS exposure.STUDY DESIGN: Pregnant Sprague-Dawley dams were gavaged with 0, 5, and 20 mg/kg body weight PFOS daily from gestational day 12-18. On gestational day 18, pregnant dams were euthanized, placentas, and fetuses were collected.MAIN OUTCOME MEASURES: Body weights of fetuses and placentas were measured, the corticosterone levels in fetal serum, and 11β-hydroxysteroid dehydrogenase 2 as well as the placental gene profiling were analyzed.RESULTS: 20 mg/kg PFOS significantly reduced fetal body weight and placental weight. Both 5 and 20 mg/kg PFOS increased fetal serum corticosterone levels. PFOS potently inhibited placental 11β-hydroxysteroid dehydrogenase 2 activity. Of 21910 genes, 45 genes were significantly downregulated ≥2 fold by 20 mg/kg PFOS, including extracellular matrix (Slpi and Pi16), growth factors and hormones (Trh and Pdf), ion transporters (Aqp1, S100a4, and Abp1), signal transducers (Kap and Ampd3), and structural constituents (A2m and Des).CONCLUSIONS: PFOS exposure may alter placental development and function, causing intrauterine growth restriction via inhibiting placental 11β-hydroxysteroid dehydrogenase 2	●	●		●						-		B	B
1195	実験動物（生殖発生毒性）	Li, Yufei; Ramdhan, Doni Hikmat; Naito, Hisao; Yamagishi, Nozomi; Ito, Yuki; Hayashi, Yumi; Yanagiba, Yukie; Okamura, Ai; Tamada, Hazuki; Gonzalez, Frank J; Nakajima, Tamie	Ammonium perfluorooctanoate may cause testosterone reduction by adversely affecting testis in relation to PPARα	2019	Toxicol Lett. 2011 Sep 10;205(3):265-72. doi: 10.1016/j.toxlet.2011.06.015. Epub 2011 Jun 25.	Perfluorooctanoate, a peroxisome proliferator-activated receptor alpha (PPARα) agonist, has the potential to lower testosterone levels as a result of testicular toxicity. To elucidate the mechanism and impact of PPARα on this reproductive toxicity, ammonium perfluorooctanoate (APFO) at doses of 0, 1.0 (low) mg/kg/day, or 5.0 (high) mg/kg/day was orally given daily to 129/sv wild-type (mPPARα), Pparα-null and PPARα-humanized (hPPARα) mice for 6 weeks. Both low- and high-dose APFO significantly reduced plasma testosterone concentrations in mPPARα and hPPARα mice, respectively. These decreases may, in part, be associated with decreased expression of mitochondrial cytochrome P450 side-chain cleavage enzyme, steroidogenic acute regulatory protein or peripheral benzodiazepine receptor as well as microsomal cytochrome P450(17α) involved in the steroidogenesis. Additionally, both doses increased abnormalities in sperm morphology and vacuolated cells in the seminiferous tubules of both mouse lines. In contrast, APFO caused only a marginal effect either on the testosterone synthesis system or sperm and testis morphology in Pparα-null mice. These results suggest that APFO may disrupt testosterone biosynthesis by lowering the delivery of cholesterol into the mitochondria and decreasing the conversion of cholesterol to pregnenolone and androstandione in the testis of mPPARα and hPPARα mice, which may, in part, be related to APFO-induced mitochondrial damage.	●	●	●	●		●			●	-		C	C
1196	実験動物（生殖発生毒性）	Liang, X.; Xie, G.; Wu, X.; Su, M.; Yang, B.	Effect of prenatal PFOS exposure on liver cell function in neonatal mice	2019	Environ Sci Pollut Res Int. 26: 18240-18246. doi: 10.1007/s11356-019-05245-4. Epub 2019 Apr 30.	Perfluorooctane sulfonate (PFOS), a hepatotoxic pollutant, is detected in the human cord blood, and it may induce health risk to an embryo. In this study, we established intrauterine exposure to PFOS in mice to evaluate potential impacts of PFOS on postnatal day 1 (PND1) offspring through conducting biochemical tests, quantitative PCR, and immunostaining. As results, PFOS-exposed maternal mice showed marked hepatomegaly and induced liver steatosis in a high dose of 5 mg PFOS/kg. In PND1 mice, intrahepatic contents of triglyceride, total cholesterol, and LDL were elevated by high-dose PFOS exposure, while intracellular HDL content was decreased. As shown in quantitative PCR, functional messenger RNAs of cytochrome P4A14 (CYP4A14) for fatty acid oxidation, CD36 for hepatic fatty acid uptake, and apolipoprotein B100 (APOB) and fibroblast growth factor 21 (FGF21) for hepatic export of lipids in PND1 livers were changed when compared to those in PFOS-free controls. In further validations, immunofluorescence stains showed that hepatic CYP4A14 and CD36 immunoreactive cells were increased in PFOS-exposed PND1 mice. In addition, reduced immunofluorescence-positive cells of APOB and FGF21 were observed in PND1 livers. Collectively, these preliminary findings demonstrate that prenatal exposure to PFOS may affect lipid metabolism in liver cells of PND1 mice.	●	●	●							-		C	C
1197	実験動物（生殖発生毒性）	Liu, L.; Liu, W.; Song, J.; Yu, H.; Jin, Y.; Oami, K.; Sato, I.; Saito, N.; Tsuda, S.	A comparative study on oxidative damage and distributions of perfluorooctane sulfonate (PFOS) in mice at different postnatal developmental stages	2009	J Toxicol Sci. 34: 245-254. doi: 10.2131/jts.34.245.	Effects of perfluorooctane sulfonate (PFOS) on maleic dialdehyde (MDA) content, superoxide dismutase (SOD) activity and total antioxidation capability (T-AOC) were compared in mice at different postnatal developmental stages, and concentrations and distributions of PFOS in different tissues were measured simultaneously. The male and female mice at postnatal day (PD) 7, PD 14, PD 21, PD 28 and PD 35 were distributed randomly to dosage group (50 mg/kg body weight) and control group (0 mg/kg body weight). Mice were administered with PFOS by once subcutaneous injection. Subsequently, after 24 hr, MDA content, SOD activity and T-AOC in brain and liver were analyzed. The PFOS concentrations in blood, brain and liver were determined by high-performance liquid chromatography negative electrospray tandem mass spectrometry (LC-MS). PFOS induced degression of the body weights of mice evidently and increase of relative weights of liver. Meanwhile, it depressed the SOD activity and T-AOC in brain and liver. The concentrations and distribution percentages of PFOS in blood, brain and liver of mice were significantly different at various postnatal developmental stages. Achieved results in this study indicate that younger mice pups were more sensitive to PFOS exposure. In addition, significant distinctions in concentrations and distribution percentages of PFOS in various tissues were demonstrated in this study. The gender difference observed was greater in the older mice. Thus it is worth giving attention especially to adverse effects of PFOS on foetus and children.	●	●		●	●					-		C	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1198	ヒト（生殖発生毒性）	Liu, X.; Chen, D.; Wang, B.; Xu, F.; Pang, Y.; Zhang, L.; Zhang, Y.; Jin, L.; Li, Z.; Ren, A.	Does Low Maternal Exposure to Per- and Polyfluoroalkyl Substances Elevate the Risk of Spontaneous Preterm Birth? A Nested Case-Control Study in China	2020	Environ Sci Technol. 2020 Jul 7;54(13):8259-8268. doi: 10.1021/acs.est.0c01930. Epub 2020 Jun 18.	Previous animal and human studies suggest potential links between maternal exposure to per- and polyfluoroalkyl substances (PFASs) and adverse birth outcomes. As spontaneous preterm birth (SPB) represents a major cause of infant mortality and precursor to future morbidity, we conducted a prospective nested case-control study in Shanxi Province, China to investigate the association between prenatal PFAS exposure and SPB risk, as well as the associations with biomarkers of oxidative stress and systemic inflammation. Among 4229 women enrolled during 2009-2013, 144 SPB cases and 375 controls were included in this study. Seventeen PFASs, as well as monocyte chemoattractant protein-1 (MCP-1), interleukin-8 (IL-8), and heme oxygenase-1 (HO-1), were measured in maternal plasma or serum collected during 4th-22nd gestational weeks. Perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), and its alternative chlorinated polyfluoroether sulfonic acid (6:2 Cl-PFESA) were detected in more than 90% samples with a median concentration of 0.79, 1.79, and 0.34 ng/mL, respectively. The analyses revealed no significant associations between plasma PFASs and the SPB risk after adjusting for potential confounders. However, concentrations of PFOS and 6:2 Cl-PFESA were both significantly and positively associated with MCP-1 levels, while PFOA was inversely associated with IL-8. Our findings suggested that maternal exposure to the determined low levels of PFAS did not induce an elevated risk of SPB, but the exposure may disturb potential biochemical pathways of inflammation. The latter has important implications for possible birth outcome effects and developmental effects in fetuses and newborns, which warrants close attention.	●	●								-		C	-
1199	実験動物（生殖発生毒性）	Lopez-Doval, S.; Salgado, R.; Fernandez-Perez, B.; Lafuente, A.	Possible role of serotonin and neuropeptide Y on the disruption of the reproductive axis activity by perfluorooctane sulfonate	2015	Toxicol Lett. 233: 138-147. doi: 10.1016/j.toxlet.2015.01.012. Epub 2015 Jan 23.	Perfluorooctane sulfonate (PFOS) is an endocrine disruptor, whose exposure can induce several alterations on the reproductive axis activity in males during adulthood. This study was undertaken to evaluate the possible role of serotonin and neuropeptide Y (NPY) on the disruption of the hypothalamic-pituitary-testicular (HPT) axis induced by PFOS in adult male rats. For that, adult male rats were orally treated with 0.5; 1.0; 3 and 6.0mg of PFOS/kg/day for 28 days. After PFOS exposure, serotonin concentration increased in the anterior and mediobasal hypothalamus as well as in the median eminence. The metabolism of this amine (expressed as the ratio 5-hydroxyindolacetic acid (5-HIAA)/serotonin) was diminished except in the anterior hypothalamus, with the doses of 3 and 6 mg/kg/day, being this dose 0.5 mg/kg/day in the median eminence. In general terms, PFOS-treated rats presented a decrease of the hypothalamic concentration of the gonadotropin releasing hormone (GnRH) and NPY. A diminution of the serum levels of the luteinizing hormone (LH), testosterone and estradiol were also shown. These results suggest that both serotonin and NPY could be involved in the inhibition induced by PFOS on the reproductive axis activity in adult male rats. (C) 2015 Elsevier Ireland Ltd. All rights reserved.	●	●								-		C	C
1200	in vitro（生殖毒性）	Lu, Yin; Luo, Bin; Li, Jing; Dai, Jiayin	Perfluorooctanoic acid disrupts the blood-testis barrier and activates the TNFα/p38 MAPK signaling pathway in vivo and in vitro	2016	Arch Toxicol. 2016 Apr;90(4):971-83. doi: 10.1007/s00204-015-1492-y. Epub 2015 Mar 6.	Perfluorooctanoic acid (PFOA) is correlated with male reproductive dysfunction in animals and humans, but the underlying mechanisms for this remain unknown. To explore the potential reproductive toxicity of PFOA, we studied blood-testis barrier (BTB) damage using in vivo and in vitro models. Male mice were gavage-administered PFOA (0-20 mg/kg/d) for 28 consecutive days, and breeding capacity and permeability of the Sertoli cell-based BTB were estimated. Primary Sertoli cells (SCs) were exposed to PFOA (0-500 μM) for 48 h, and transepithelial electrical resistance (TER) was assessed. Furthermore, BTB-associated protein expression, TNFα content, and phosphorylation and protein levels of the mitogen-activated protein kinase (MAPK) pathway were detected. An apparent decrease in mated and pregnant females per male mouse as well as litter weight was observed. Marked BTB damage was evidenced by increased red biotin fluorescence in the lumen tubular of the testes and the decrease in TER in SCs in vitro. The protein levels of claudin-11, connexin-43, N-cadherin, β-catenin, and occludin were significantly decreased in the testes and also in the SCs in vitro except for N-cadherin and β-catenin. TNFα content showed a dose-dependent increase in the testes and a dose- and time-dependent increase in the SCs, with the p-p38/p38 MAPK ratio also increasing in testes and SCs after PFOA exposure. Moreover, PFOA altered expressions of claudin-11, connexin-43, TNFα, and p-p38 MAPK were recovered 48 h after PFOA removal in the SCs. The SCs appeared to be target to PFOA, and the disruption of the BTB may be crucial to PFOA-induced reproductive dysfunction in mice.	●	●							●	-		C	C
1201	実験動物（生殖発生毒性）	Lu, Yin; Pan, Yitao; Sheng, Nan; Zhao, Allan Z; Dai, Jiayin	Perfluorooctanoic acid exposure alters polyunsaturated fatty acid composition, induces oxidative stress and activates the AKT/AMPK pathway in mouse epididymis	2016	Chemosphere. 2016 Sep;158:143-53. doi: 10.1016/j.chemosphere.2016.05.071. Epub 2016 Jun 1.	Perfluorooctanoic acid (PFOA) is a degradation-resistant compound with a carbon-fluorine bond. Although PFOA emissions have been reduced since 2000, it remains persistent in the environment. Several studies on laboratory animals indicate that PFOA exposure can impact male fertility. Here, adult male mice received either PFOA (1.25, 5 or 20 mg/kg/d) or an equal volume of water for 28 d consecutively. PFOA accumulated in the epididymis in a dose-dependent manner and resulted in reduced epididymis weight, lower levels of triglycerides (TG), cholesterol (CHO), and free fatty acids (FFA), and activated AKT/AMPK signaling in the epididymis. Altered polyunsaturated fatty acid (PUFA) compositions, such as a higher arachidonic acid:linoleic acid (AA:LA) ratio, concomitant with excessive oxidative stress, as demonstrated by increased malonaldehyde (MDA) and decreased glutathione peroxidase (GSH-Px) in the epididymis, were observed in epididymis tissue following treatment with PFOA. These results indicate that the epididymis is a potential target of PFOA. Oxidative stress and PUFA alteration might help explain the sperm injury and male reproductive dysfunction induced by PFOA exposure.	●	●								-		C	C
1202	実験動物（生殖発生毒性）	Luebker, D. J.; Case, M. T.; York, R. G.; Moore, J. A.; Hansen, K. J.; Butenhoff, J. L.	Two-generation reproduction and cross-foster studies of perfluorooctanesulfonate (PFOS) in rats	2005	Toxicology. 2005 Nov 5;215(1-2):126-48. doi: 10.1016/j.tox.2005.07.018.	Perfluorooctanesulfonate (PFOS) is a persistent acid found widely distributed in wildlife and humans. To understand the potential reproductive and developmental effects of PFOS, a two-generation reproduction study was conducted in rats. Male and female rats were dosed via oral gavage at dose levels of 0, 0.1, 0.4, 1.6, and 3.2 mg/(kg day) for 6 weeks prior to mating, during mating, and, for females, through gestation and lactation, across two generations. Due to substantial F1 neonatal toxicity observed in the 1.6 and 3.2 mg/(kg day) groups, continuation into the second generation was limited to F1 pups from the 0, 0.1, and 0.4 mg/(kg day) groups. No adverse effects were observed in F0 females or their fetuses upon caesarean sectioning at gestation day 10 Statistically significant reductions in body-weight gain and feed consumption were observed in F0 generation males and females at dose levels of 0.4 mg/(kg day) and higher, but not in F1 adults. PFOS did not affect reproductive performance (mating, estrous cycling, and fertility); however, reproductive outcome, as demonstrated by decreased length of gestation, number of implantation sites, and increased numbers of dams with stillborn pups or with all pups dying on lactation days 1-4, was affected at 3.2 mg/(kg day) in F0 dams. These effects were not observed in F1 dams at the highest dose tested, 0.4 mg/(kg day). Neonatal toxicity in F1 pups, as demonstrated by reduced survival and body-weight gain through the end of lactation, occurred at a maternal dose of 1.6 mg/(kg day) and higher while not at dose levels of 0.1 or 0.4 mg/(kg day) or in F2 pups at the 0.1 or 0.4 mg/(kg day) dose levels tested. In addition to these adverse effects, slight yet statistically significant developmental delays occurred at 0.4 (eye opening) and 1.6 mg/(kg day) (eye opening, air righting, surface righting, and pinna unfolding) in F1 pups. Based on these data, the NOAELs were as follows: reproductive function: F0> or 3.2 and F1> or 0.4 mg/(kg day); reproductive outcome: F0=1.6 and F1> or 0.4 mg/(kg day); overall parental effects: F0=0.1 and F1> or 0.4 mg/(kg day); offspring effects: F0=0.4 and F1> or 0.4 mg/(kg day). To distinguish between maternal and pup influences contributing to the perinatal mortality observed in the two-generation study, a follow-up cross-foster study was performed. Results of this study indicated that in utero exposure to PFOS causally contributed to post-natal pup mortality, and that pre-natal and post-natal	●	●	●	●	●		●		●	-	1	A	A
1203	実験動物（生殖発生毒性）	Luebker, D. J.; York, R. G.; Hansen, K. J.; Moore, J. A.; Butenhoff, J. L.	Neonatal mortality from in utero exposure to perfluorooctanesulfonate (PFOS) in Sprague-Dawley rats: dose-response, and biochemical and pharamacokinetic parameters	2005	Toxicology. 2005 Nov 5;215(1-2):149-69. doi: 10.1016/j.tox.2005.07.019. Epub 2005 Aug 29.	Perfluorooctanesulfonate (PFOS) is a widely distributed, environmentally persistent acid found at low levels in human, wildlife, and environmental media samples. Neonatal mortality has been observed following PFOS exposure in a two-generation reproduction study in rats and after dosing pregnant rats and mice during gestation. Objectives of the current study were to better define the dose-response curve for neonatal mortality in rat pups born to PFOS-exposed dams and to investigate biochemical and pharmacokinetic parameters potentially related to the etiology of effects observed in neonatal rat pups. In the current study, additional doses of 0.8, 1.0, 1.2, and 2 mg/kg/day were included with original doses used in the two-generation study of 0.4 and 1.6 mg/kg/day in order to obtain data in the critical range of the dose-response curve. Biochemical parameters investigated in dams and litters included: -1 serum lipids, glucose, mevalonic acid, and thyroid hormones; -2 milk cholesterol; and -3 liver lipids. Pharmacokinetic parameters investigated included the interrelationship of administered oral dose of PFOS to maternal body burden of PFOS and the transfer of maternal body burden to the fetus in utero and pup during lactation, as these factors may affect neonatal toxicity. Dosing of dams occurred for 6 weeks prior to mating with untreated breeder males, through confirmed mating, gestation, and day four of lactation. Dose levels for the dose-response and etiological investigation were 0.0, 0.4, 0.8, 1.0, 1.2, 1.6, and 2 mg/kg/day PFOS. Statistically significant decreases in gestation length were observed in the 0.8 mg/kg and higher dose groups. Decreases in viability through lactation day 5 were observed in the 0.8 mg/kg and higher dose groups, becoming statistically significant in the 1.6 and 2 mg/kg dose groups. Reduced neonatal survival did not appear to be the result of reductions in lipids, glucose utilization, or thyroid hormones. The endpoints of gestation length and decreased viability were positively correlated, suggesting that late-stage fetal development may be affected in pups exposed to PFOS in utero and may contribute to the observed mortality. Benchmark dose (BMD) estimates for decreased gestation length, birth weight, pup weight on lactation day 5, pup weight gain through lactation day 5, and viability resulted in values ranging from 0.27 to 0.89mg/kg/day for the lower 0.95 confidence limit of the BMD5 (BMDL5). Results of analyses for PFOS in biological matrices indicate a linear proportionality of mean serum PFOS concentration to maternal administered dose prior to mating and through the first	●	●	●	●	●		●		●	-	1	A	A

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1204	実験動物（生殖発生毒性）	Macon, Madisa B; Fenton, Suzanne E	Endocrine disruptors and the breast: Early life effects and later life disease [Review]	2013	J Mammary Gland Biol Neoplasia. 2013 Mar;18(1):43-61. doi: 10.1007/s10911-013-9275-7. Epub 2013 Feb 17.	Breast cancer risk has both heritable and environment/lifestyle components. The heritable component is a small contribution (5-27 %), leaving the majority of risk to environment (e.g., applied chemicals, food residues, occupational hazards, pharmaceuticals, stress) and lifestyle (e.g., physical activity, cosmetics, water source, alcohol, smoking). However, these factors are not well-defined, primarily due to the enormous number of factors to be considered. In both humans and rodent models, environmental factors that act as endocrine disrupting compounds (EDCs) have been shown to disrupt normal mammary development and lead to adverse lifelong consequences, especially when exposures occur during early life. EDCs can act directly or indirectly on mammary tissue to increase sensitivity to chemical carcinogens or enhance development of hyperplasia, beaded ducts, or tumors. Protective effects have also been reported. The mechanisms for these changes are not well understood. Environmental agents may also act as carcinogens in adult rodent models, directly causing or promoting tumor development, typically in more than one organ. Many of the environmental agents that act as EDCs and are known to affect the breast are discussed. Understanding the mechanism(s) of action for these compounds will be critical to prevent their effects on the breast in the future.	●	●								-		C	C
1205	実験動物（生殖発生毒性）	Macon, Madisa B; Villanueva, LaTonya R; Tatum-Gibbs, Katoria; Zehr, Robert D; Strynar, Mark J; Stanko, Jason P; White, Sally S; Helfant, Laurence; Fenton, Suzanne E	Prenatal perfluorooctanoic acid exposure in CD-1 mice: low-dose developmental effects and internal dosimetry	2011	Toxicol Sci. 2011 Jul;122(1):134-45. doi: 10.1093/toxsci/kfr076. Epub 2011 Apr 11.	Perfluorooctanoic acid (PFOA) is an environmental contaminant that causes adverse developmental effects in laboratory animals. To investigate the low-dose effects of PFOA on offspring, timed-pregnant CD-1 mice were gavage dosed with PFOA for all or half of gestation. In the full-gestation study, mice were administered 0, 0.3, 1.0, and 3.0 mg PFOA/kg body weight (BW)/day from gestation days (GD) 1-17. In the late-gestation study, mice were administered 0, 0.01, 0.1, and 1.0 mg PFOA/kg BW/day from GD 10-17. Exposure to PFOA significantly ($p < 0.05$) increased offspring relative liver weights in all treatment groups in the full-gestation study and in the 1.0 mg PFOA/kg group in the late-gestation study. In both studies, the offspring of all PFOA-treated dams exhibited significantly stunted mammary epithelial growth as assessed by developmental scoring. At postnatal day 21, mammary glands from the 1.0 mg/kg GD 10-17 group had significantly less longitudinal epithelial growth and fewer terminal end buds compared with controls ($p < 0.05$). Evaluation of internal dosimetry in offspring revealed that PFOA concentrations remained elevated in liver and serum for up to 6 weeks and that brain concentrations were low and undetectable after 4 weeks. These data indicate that PFOA-induced effects on mammary tissue (1) occur at lower doses than effects on liver weight in CD-1 mice, an observation that may be strain specific, and (2) persist until 12 weeks of age following full-gestational exposure. Due to the low-dose sensitivity of mammary glands to PFOA in CD-1 mice, a no observable adverse effect level for mammary developmental delays was not identified in these studies.	●	●	●	●		●	●		●	-		B	B
1206	実験動物（生殖発生毒性）	Mann, PC; Frame, SR.	FC-143: Two year oral toxicity-oncogenicity study in rats	2004	U.S. Environmental Protection Agency Administrative Record 226.	No abstract available	●	●		●					●	企業データ		D	D
1207	実験動物（生殖発生毒性）	Mshaty, A.; Haijima, A.; Takatsuru, Y.; Ninomiya, A.; Yajima, H.; Kokubo, M.; Khairinisa, M. A.; Miyazaki, W.; Amano, I.; Koibuchi, N.	Neurotoxic effects of lactational exposure to perfluorooctane sulfonate on learning and memory in adult male mouse	2020	Food Chem Toxicol. 2020 Nov;145:111710. doi: 10.1016/j.fct.2020.111710. Epub 2020 Aug 28.	The present study aims to examine the effect of early lactational perfluorooctane sulfonate (PFOS) exposures on learning and memory in male mice and reveal the underlying mechanisms involved. PFOS solution was orally administered to dams from the postpartum days 1 to 14, so that pups would be exposed through breast milk. At 44783 weeks of age, we performed object location test (OLT), object recognition test (ORT), and pairwise visual discrimination (VD) task. We also performed in vivo microdialysis, and mRNA and protein analysis of genes responsible for hippocampal development and function. In both OLT and ORT, the performance of mice in the PFOS-exposed group was significantly lower than those in the control group. In the VD task, the PFOS-exposed group learned significantly slower than the control group. Concentrations of glutamate and gamma-aminobutyric acid in the dorsal hippocampus were significantly higher in the PFOS-exposed group than in the control group. No notable differences were shown in our mRNA and protein studies. The present study showed that lactational PFOS exposure has a profound, long-lasting neurotoxic effect in the hippocampus and consequently leads to learning and memory deficits.	●	●								-		B	B
1208	実験動物（生殖発生毒性）	Ngo, H. T.; Hetland, R. B.; Sabaredzovic, A.; Haug, L. S.; Steffensen, I. L.	In utero exposure to perfluorooctanoate (PFOA) or perfluorooctane sulfonate (PFOS) did not increase body weight or intestinal tumorigenesis in multiple intestinal neoplasia (Min/+) mice	2014	Environ Res. 132: 251-263. doi: 10.1016/j.envres.2014.03.033. Epub 2014 May 13.	We examined whether perfluorooctanoate (PFOA) or perfluorooctane sulfonate (PFOS) had obesogenic effects and if they increased spontaneous intestinal tumorigenesis in the mouse model C57BL/6J-Min/+ (multiple intestinal neoplasia) after in utero exposure. The dams were exposed to PFOA or PFOS (0.01, 0.1 or 3.0mg/kg bw/day) by po gavage on GD1-17. The Min/+ and wild-type offspring were terminated at week 11 for examination of intestinal tumorigenesis or at week 20 for obesogenic effect, respectively. Body weights of the dams and pups were recorded throughout life. Food intake was determined at week 6 and 10 Blood glucose (non-fasted) was measured at week 6 and 11 No obesogenic effect of PFOA or PFOS was observed up to 20 weeks of age. PFOA or PFOS did not increase the incidence or number of tumors in the small intestine or colon of the Min/+ mice or affect their location along the intestines. Feed intake was not affected. There were some indications of toxicity of PFOA, but not of PFOS. There was lower survival of pups after 3.0mg/kg PFOA, lower body weight in pups after 3 and possibly 0.1mg/kg PFOA, and increased relative liver weight after 0.01 and possibly 0.1mg/kg PFOA. Plasma glucose was lower after 0.01	●	●	●	●						-		C	B
1209	実験動物（生殖発生毒性）	Onishchenko, N.; Fischer, C.; Wan Ibrahim, W. N.; Negri, S.; Spulber, S.; Cottica, D.; Ceccatelli, S.	Prenatal exposure to PFOS or PFOA alters motor function in mice in a sex-related manner	2011	Neurotox Res. 2011 Apr;19(3):452-61. doi: 10.1007/s12640-010-9200-4. Epub 2010 May 29.	Perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) are organic surfactants widely used in various industrial and consumer applications. Due to their chemical properties, these perfluorinated compounds (PFCs) have also become persistent contaminants. The risk of possible intrauterine and lactational exposure to these chemicals poses a significant health concern for potential developmental effects. In the present study we have found that dietary exposure of mice to 0.3 mg/kg of PFOS or PFOA throughout pregnancy results in different distribution pattern in the offspring brain and liver. In particular, exposure to PFOS led to four times higher accumulation of the chemical in the brains of newborn mice than PFOA. We have used a battery of behavioral tests to evaluate motor function, circadian activity, and emotion-related behavior in the exposed offspring. Exposure to PFOS resulted in decreased locomotion in a novel environment and reduced muscle strength only in male offspring. Prenatal exposure to PFOA was associated with changes in exploratory behavior in male and female offspring, as well as with increased global activity in males in their home cage. The neurobehavioral outcome of prenatal exposure to PFCs in mice is characterized by mild alterations in motor function and it appears to be sex-related.	●	●		●	●	●			●	-		B	B
1210	実験動物（生殖発生毒性）	Qiu, L.; Qian, Y.; Liu, Z.; Wang, C.; Qu, J.; Wang, X.; Wang, S.	Perfluorooctane sulfonate (PFOS) disrupts blood-testis barrier by down-regulating junction proteins via p38 MAPK/ATF2/MMP9 signaling pathway	2016	Toxicology. 373: 1-12. doi: 10.1016/j.tox.2016.11.003. Epub 2016 Nov 3.	Perfluorooctane sulfonate (PFOS), an ubiquitous environmental pollutant, has been associated with male reproductive disorders. However, the underlying mechanisms are not yet fully understood. In this study, in vivo and in vitro models were used to explore the effects of PFOS on blood-testis barrier (BTB) and related molecular mechanisms. First, male ICR mice were orally administrated PFOS (0.5-10mg/kg/bw) for 4 weeks. Bodyweight, sperm count, BTB integrity and the expression of proteins including p38 mitogen-activated protein kinase (MAPK), activating transcription factor 2 (ATF2), matrix metalloproteinase 9 (MMP9), tissue inhibitor of metalloproteinase 1(TIMP1) and BTB related junction proteins were evaluated. Furthermore, mouse primary Sertoli cells were used to delineate the molecular mechanisms that mediate the effects of PFOS on BTB. Our results demonstrated that PFOS dose-dependently increased BTB permeability, p38/ATF2 phosphorylation and MMP9 expression, paralleled by decrease in BTB junction protein Occludin and Connexin43 expression. Additionally, similar to the in vivo results, treatment of PFOS time-dependently increased Sertoli cell-based BTB permeability, phosphorylated-p38/ATF2 level, translocation of ATF2 into the nucleus and MMP9 expression/activity, paralleled by decrease in Occludin and Connexin43 expression. Meanwhile, inhibition of p38 by SB203580, knockdown of ATF2, or inhibition of MMP9 was sufficient to reduce the effects of PFOS on the Sertoli cell BTB. As such, the present study highlights a role of the p38/ATF2/MMP9 signaling pathway in PFOS-induced BTB disruption, advancing our understanding of molecular mechanisms for PFOS-induced male reproductive disorders.	●	●								-		C	C
1211	実験動物（生殖発生毒性）	Qiu, L.; Zhang, X.; Zhang, X.; Zhang, Y.; Gu, J.; Chen, M.; Zhang, Z.; Wang, X.; Wang, S. L.	Sertoli cell is a potential target for perfluorooctane sulfonate-induced reproductive dysfunction in male mice	2013	Toxicol Sci. 2013 Sep;135(1):229-40. doi: 10.1093/toxsci/kft129. Epub 2013 Jun 12.	Perfluorooctane sulfonate (PFOS) is associated with male reproductive disorders, but its targets and mechanisms are poorly understood. We used in vitro and in vivo models to explore the roles of Sertoli cells and the blood-testis barrier (BTB) in PFOS-induced male reproductive dysfunction. First, we used primary Sertoli cell to estimate PFOS-induced cytotoxicity, junction proteins expression, and the changes of barrier function. ICR mice were then administered PFOS (0.25-50mg/kg/day) for 4 weeks. Sperm count, ultrastructure and permeability of the Sertoli cell-based BTB, and testicular PFOS were estimated. Furthermore, the expression and localization of proteins related to junctions between Sertoli cells and mitogen-activated protein kinase (MAPK) signaling pathway were evaluated. Apparent decreases in sperm count were found. PFOS significantly increased vacuolization in Sertoli cells in seminiferous tubules and BTB ultrastructural disassembly, which subsequently increased BTB permeability and testicular PFOS levels, which was confirmed by in vitro results that PFOS decreased transepithelial electrical resistance between Sertoli cells. Additionally, PFOS decreased the expression of junction proteins in Sertoli cells, which was further confirmed by in vivo results that PFOS decreased or dislocated junction proteins (i.e., ZO-1, occludin, claudin-11, and connexin-43) and increased proteins related to the MAPK signaling pathway (i.e., Erk and p38), whereas basal ectoplasmic specialization proteins did not change. The results were confirmed by SB203580, a p38 MAPK selective inhibitor. Sertoli cells appear to be a new cellular target for PFOS. Together with disruption of BTB integrity and function, these cells play an important role in PFOS-induced male reproductive toxicity.	●	●								-		C	C
1212	実験動物（生殖発生毒性）	Qu, J. H.; Lu, C. C.; Xu, C.; Chen, G.; Qiu, L. L.; Jiang, J. K.; Ben, S.; Wang, Y. B.; Gu, A. H.; Wang, X. R.	Perfluorooctane sulfonate-induced testicular toxicity and differential testicular expression of estrogen receptor in male mice	2016	Environ Toxicol Pharmacol. 2016 Jul;45:150-7. doi: 10.1016/j.etap.2016.05.025. Epub 2016 May 31.	Perfluorooctane sulfonate (PFOS, CAS#1763-23-1) causes male reproductive toxicities, but the underlying mechanisms are still unclear. In this study, 0, 0.5 and 10mg/kg/day PFOS were given by oral gavage to adult mice for 5 weeks. In the 10mg/kg group, serum testosterone levels decreased significantly. Sperm counts declined which might be associated with the decreased proliferation and increased apoptosis of germ cells. In relation to increased apoptosis, bax, cleaved caspase-9 and cleaved caspase-3 levels elevated significantly, indicating that PFOS induced germ cell apoptosis by activating the mitochondrial pathway. In addition, the increase in levels of testicular estrogen receptor (ER) β was observed in both 0.5 and 10mg/kg group, whereas a decrease in ERα expression was only observed in 10mg/kg group. These results suggested that the alterations in testicular ERs expression, together with decreased proliferation and increased apoptosis of germ cells, might be involved in PFOS-induced testicular toxicity.	●	●		●						-		C	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1213	実験動物（生殖発生毒性）	Quist, E. M.; Filgo, A. J.; Cummings, C. A.; Kissling, G. E.; Hoenerhoff, M. J.; Fenton, S. E.	Hepatic mitochondrial alteration in CD-1 mice associated with prenatal exposures to low doses of perfluorooctanoic acid	2015	Toxicol Pathol. 43: 546-557. doi: 10.1177/0192623314551841. Epub 2014 Oct 16.	Perfluorooctanoic acid (PFOA) is a perfluoroalkyl acid primarily used as an industrial surfactant. It persists in the environment and has been linked to potentially toxic and/or carcinogenic effects in animals and people. As a known activator of peroxisome proliferator-activated receptors (PPARs), PFOA exposure can induce defects in fatty acid oxidation, lipid transport, and inflammation. Here, pregnant CD-1 mice were orally gavaged with 0, 0.01, 0.1, 0.3, and 1 mg/kg of PFOA from gestation days (GD) 1 through 17 On postnatal day (PND) 21, histopathologic changes in the livers of offspring included hepatocellular hypertrophy and periportal inflammation that increased in severity by PND 91 in an apparent dose-dependent response. Transmission electron microscopy (TEM) of selected liver sections from PND 91 mice revealed PFOA-induced cellular damage and mitochondrial abnormalities with no evidence of peroxisome proliferation. Within hypertrophied hepatocytes, mitochondria were not only increased in number but also exhibited altered morphologies suggestive of increased and/or uncontrolled fission and fusion reactions. These findings suggest that peroxisome proliferation is not a component of PFOA-induced hepatic toxicity in animals that are prenatally exposed to low doses of PFOA.	●	●		●		●				-		C	B
1214	実験動物（生殖発生毒性）	Rogers, J. M.; Ellis-Hutchings, R. G.; Grey, B. E.; Zucker, R. M.; Norwood, J., Jr; Grace, C. E.; Gordon, C. J.; Lau, C.	Elevated blood pressure in offspring of rats exposed to diverse chemicals during pregnancy	2014	Toxicol Sci. 137: 436-446. doi: 10.1093/toxsci/kft248. Epub 2013 Nov 11.	Adverse intrauterine environments have been associated with increased risk of later cardiovascular disease and hypertension. In an animal model using diverse developmental toxicants, we measured blood pressure (BP), renal nephron endowment, renal glucocorticoid receptor (GR) gene expression, and serum aldosterone in offspring of pregnant Sprague-Dawley rats exposed to dexamethasone (Dex), perfluorooctane sulfonate (PFOS), atrazine, perfluorononanoic acid (PFNA), arsenic or nicotine. BP was assessed by tail cuff photoplethysmography, nephron endowment by confocal microscopy, and renal GR mRNA by qPCR. BP was also measured by telemetry, and corticosterone (CORT) was measured in resting or restrained Dex and atrazine offspring. Treated dams gained less weight during treatment in all groups except arsenic. There were chemical- and sex-specific effects on birth weight, but offspring body weights were similar by weaning. BP was higher in Dex, PFOS, atrazine and PFNA male offspring by 44752 weeks. Female offspring exhibited elevated BP at 10 weeks for PFNA and arsenic, and at 37 weeks for Dex, PFOS and atrazine. Dex, PFOS and atrazine offspring still exhibited elevated BP at 52-65 weeks of age; others did not. Elevated BP was associated with lower nephron counts. Dex, PFOS and atrazine offspring had elevated renal GR gene expression. Elevations in BP were also observed in Dex and atrazine offspring by radiotelemetry. Atrazine offspring exhibited enhanced CORT response to restraint. Elevated offspring BP was induced by maternal exposure to toxicants. Since all treatments affected maternal gestational weight gain, maternal stress may be a common underlying factor in these observations.	●	●	●	●	●					-		C	B
1215	実験動物（生殖発生毒性）	Salimi, A.; Nikoosiar Jahromi, M.; Pourahmad, J.	Maternal exposure causes mitochondrial dysfunction in brain, liver, and heart of mouse fetus: An explanation for perfluorooctanoic acid induced abortion and developmental toxicity	2019	Environ Toxicol. 2019 Jul;34(7):878-885. doi: 10.1002/tox.22760. Epub 2019 Apr 29.	Perfluorooctanoic acid (PFOA) is an octanoic acid and is found in wildlife and humans. We have investigated mitochondrial toxicity in isolated mitochondria from, placenta, brain, liver, and heart after oral exposure with PFOA in mice during gestational days (7-15). Histopathological examination and mitochondrial toxicity parameters were assayed. Results indicated that PFOA decreased the weight of the fetus and placenta, the length of the fetus and the diameter of the placenta, dead fetuses and dead macerated fetuses in treated mice with 25 mg/kg. Histopathological examination showed that PFOA induced pathological abnormalities in liver, brain, heart, and placenta. Also, PFOA induced mitochondria toxicity in brain, liver, heart of mouse fetus. Our results indicate that PFOA up to 20 mg/kg exposure adversely affect embryofetal/developmental because for mitochondria dysfunction. These results suggested that mitochondrial dysfunction induced by PFOA in liver, heart, and brain lead to developmental toxicity and abnormality in tissues.	●	●								-	1	A	A
1216	実験動物（生殖発生毒性）	Sobolewski, M.; Conrad, K.; Allen, J. L.; Weston, H.; Martin, K.; Lawrence, B. P.; Cory-Slechta, D. A.	Sex-specific enhanced behavioral toxicity induced by maternal exposure to a mixture of low dose endocrine-disrupting chemicals	2014	Neurotoxicology. 45: 121-130. doi: 10.1016/j.neuro.2014.09.008. Epub 2014 Oct 22.	Humans are increasingly and consistently exposed to a variety of endocrine disrupting chemicals (EDCs), chemicals that have been linked to neurobehavioral disorders such as ADHD and autism. Many of such EDCs have been shown to adversely influence brain mesocorticolimbic systems raising the potential for cumulative toxicity. As such, understanding the effects of developmental exposure to mixtures of EDCs is critical to public health protection. Consequently, this study compared the effects of a mixture of four EDCs to their effects alone to examine potential for enhanced toxicity, using behavioral domains and paradigms known to be mediated by mesocorticolimbic circuits (fixed interval (FI) schedule controlled behavior, novel object recognition memory and locomotor activity) in offspring of pregnant mice that had been exposed to vehicle or relatively low doses of four EDCs, atrazine (ATR - 10mg/kg), perfluorooctanoic acid (PFOA - 0.1mg/kg), bisphenol-A (BPA - 50 μg/kg), 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD - 0.25 μg/kg) alone or combined in a mixture (MIX), from gestational day 7 until weaning. EDC-treated males maintained significantly higher horizontal activity levels across three testing sessions, indicative of delayed habituation, whereas no effects were found in females. Statistically significant effects of MIX were seen in males, but not females, in the form of increased FI response rates, in contrast to reductions in response rate with ATR, BPA and TCDD, and reduced short term memory in the novel object recognition paradigm. MIX also reversed the typically lower neophobia levels of males compared to females. With respect to individual EDCs, TCDD produced notable increases in FI response rates in females, and PFOA significantly increased ambulatory locomotor activity in males. Collectively, these findings show the potential for enhanced behavioral effects of EDC mixtures in males and underscore the need for animal studies to fully investigate mixtures, including chemicals that converge on common physiological substrates to examine potential mechanisms of toxicity with full dose effect curves to assist in interpretations of relevant mechanisms.	●	●		●						-		C	B
1217	実験動物（生殖発生毒性）	Song, P.; Li, D.; Wang, X.; Zhong, X.	Effects of perfluorooctanoic acid exposure during pregnancy on the reproduction and development of male offspring mice	2018	Andrologia. 50: e13059. doi: 10.1111/and.13059. Epub 2018 Jun 3.	This study was conducted to explore the effects of maternal exposure to perfluorooctanoic acid (PFOA) on reproduction and development of male offspring mice. Pregnant mice were given 1, 2.5 or 5 mg/kg BW PFOA daily by gavage during gestation. The results showed that the survival number of offspring mice at weaning was significantly decreased. There were no differences in the testicular index of offspring mice between PFOA exposure groups and non-PFOA group. Maternal exposure to PFOA reduced the level of testosterone in the male offspring mice on PND 21 ($p < 0.01$) but increased in 1 mg/kg group and decreased in 2.5 and 5 mg/kg groups on PND 70 ($p < 0.01$). There were different degrees of damage to testis in a dose-dependent manner, and the number of Leydig cells markedly decreased ($p < 0.01$) in 2.5 and 5 mg/kg PFOA groups on PND 21 and PND 70 The expression of Dlk1-Dio3 imprinted gene cluster showed a decreasing trend, where Gtl2, Rian and Dio3 gene expressions were significantly reduced ($p < 0.05$) on PND 21 Therefore, PFOA exposure during pregnancy reduces the number of survival offspring mice, damages testis, disrupts reproductive hormones and reduces the mRNA expressions of the Dlk1-Dio3 imprinted cluster in testis.	●	●	●							-		B	B
1218	実験動物（生殖発生毒性）	Staples, R E; Burgess, B A; Kerns, W D	The embryo-fetal toxicity and teratogenic potential of ammonium perfluorooctanoate (APFO) in the rat	1984	Fundam Appl Toxicol. 1984 Jun;4(3 Pt 1):429-40. doi: 10.1016/0272-0590(84)90200-8.	Ammonium perfluorooctanoate (APFO, greater than 95% pure) was administered to Sprague-Dawley rats from Days 6 through 15 of gestation by inhalation as a dust (whole body exposure) for 6 hr/day at 0, 0.1, 1, 10, and 25 mg/m3, or by gavage at 100 mg/kg body wt/day in corn oil. Maternal deaths occurred in the groups given the highest level of APFO by each route and overt toxicity was evident among the surviving dams of these groups and among those of the 10-mg/m3 group. The fetuses were examined for external, visceral, and skeletal alterations and for APFO-related macroscopic and microscopic alterations of the eyes. In the postpartum period, pups from additional control and experimental dams were examined externally and ophthalmoscopically, and the usual fertility and viability indices were calculated. A teratogenic response was not demonstrated. Toxic effects on the conceptus were noted only in the groups given the highest level of APFO by each route. Hence, APFO was not demonstrated to represent a unique hazard to the conceptus of the rat.	●	●		●		●				-		C	B
1219	実験動物（生殖発生毒性）	Suh, C. H.; Cho, N. K.; Lee, C. K.; Lee, C. H.; Kim, D. H.; Kim, J. H.; Son, B. C.; Lee, J. T.	Perfluorooctanoic acid-induced inhibition of placental prolactin-family hormone and fetal growth retardation in mice	2011	Mol Cell Endocrinol. 2011 Apr 30;337(1-2):7-15. doi: 10.1016/j.mce.2011.01.009. Epub 2011 Jan 15.	Perfluorooctanoic acid (PFOA) is a persistent pollutant worldwide and even found in human cord blood and breast milk. Some animal studies have reported that PFOA causes developmental toxicity such as fetal weight loss, but the mechanism is still unclear. This study focused on developmental toxicity of PFOA, particularly impacts of PFOA on placental endocrine function such as placental prolactin (PRL)-family hormone gene expression and fetal growth in mouse. Time-mated CD-1 mice were dosed by gavage with 0, 2, 10 and 25 mg/kg B.W/day of PFOA (n-10) dissolved with de-ionized water from gestational day (GD) 11-16. During treatment, body weight of each pregnant mouse was measured daily. On day 16, caesarean sections were performed and developmental data were observed. Three placentas from three different pregnant mice were assigned to each of the following experiments. The mRNA levels of mouse placental lactogen (mPL)-II, prolactin like protein (mPLP)-E, -F and Pit-1α and β isotype mRNAs, a transacting factor of mPLs and mPLPs genes, were analyzed using northern blot, in situ hybridization and RT-PCR, respectively. Maternal body weight gain was significantly declined from GD 13 in the PFOA treated groups compared to control. Developmental data such as fetal and placental weights were significantly decreased in accordance with PFOA dosage. Number of dead fetuses and post-implantation losses were significantly increased in the PFOA-exposed groups. In addition, placental efficiency (fetal weight/placental weight) was significantly reduced in PFOA treated groups in accordance with PFOA dosage. Histopathologic changes were observed in placenta. Dose dependent necrotic changes were observed in both 10 mg and 25 mg PFOA treated groups. Cell frequency of glycogen trophoblast cell and parietal trophoblast giant cell were decreased dose dependently in the junctional zone. In the labyrinth zone, sinusoidal trophoblast giant cell frequency was decreased in the 25 mg PFOA treated group. Also, morphological change such as crushed nuclear (atrophy) of trophoblast cells was observed in 25 mg PFOA treated group. Finally, mRNA levels of the mPL-II, mPLP-E, -F and Pit-1α and β were significantly reduced in the PFOA treated groups dose dependently. In addition, the changing pattern between mPL-II, mPLP-E, -F mRNA levels and fetal body weight showed positive relationship. In conclusion, the inhibitory effects of PFOA on the placental prolactin-family hormone genes expression may be secondary effects to insufficient trophoblast cell type differentiation and/or increased trophoblast cell necrosis. The impacts of PFOA on placental development and endocrine function reduced the placental efficiency and	●	●	●	●		●			●	-		C	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報抽出対象	文献ランク①	文献ランク②
1220	実験動物（生殖発生毒性）	Thibodeaux, J. R.; Hanson, R. G.; Rogers, J. M.; Grey, B. E.; Barbee, B. D.; Richards, J. H.; Butenhoff, J. L.; Stevenson, L. A.; Lau, C.	Exposure to perfluorooctane sulfonate during pregnancy in rat and mouse. I: maternal and prenatal evaluations	2003	Toxicol Sci. 2003 Aug;74(2):369-81. doi: 10.1093/toxsci/kfg121. Epub 2003 May 28.	The maternal and developmental toxicities of perfluorooctane sulfonate (PFOS, C8F17SO3-) were evaluated in the rat and mouse. PFOS is an environmentally persistent compound used as a surfactant and occurs as a degradation product of both perfluorooctane sulfonyl fluoride and substituted perfluorooctane sulfonamido components found in many commercial and consumer applications. Pregnant Sprague-Dawley rats were given 1, 2, 3, 5, or 10 mg/kg PFOS daily by gavage from gestational day (GD) 2 to GD 20; CD-1 mice were similarly treated with 1, 5, 10, 15, and 20 mg/kg PFOS from GD 1 to GD 17 Controls received 0.005 Tween-20 vehicle (1 ml/kg for rats and 10 ml/kg for mice). Maternal weight gain, food and water consumption, and serum chemistry were monitored. Rats were euthanized on GD 21 and mice on GD 18 PFOS levels in maternal serum and in maternal and fetal livers were determined. Maternal weight gains in both species were suppressed by PFOS in a dose-dependent manner, likely attributed to reduced food and water intake. Serum PFOS levels increased with dosage, and liver levels were approximately fourfold higher than serum. Serum thyroxine (T4) and triiodothyronine (T3) in the PFOS-treated rat dams were significantly reduced as early as one week after chemical exposure, although no feedback response of thyroid-stimulating hormone (TSH) was observed. A similar pattern of reduction in T4 was also seen in the pregnant mice. Maternal serum triglycerides were significantly reduced, particularly in the high-dose groups, although cholesterol levels were not affected. In the mouse dams, PFOS produced a marked enlargement of the liver at 10 mg/kg and higher dosages. In the rat fetuses, PFOS was detected in the liver but at levels nearly half of those in the maternal counterparts, regardless of administered doses. In both rodent species, PFOS did not alter the numbers of implantations or live fetuses at term, although small deficits in fetal weight were noted in the rat. A host of birth defects, including cleft palate, anasarca, ventricular septal defect, and enlargement of the right atrium, were seen in both rats and mice, primarily in the 10 and 20 mg/kg dosage groups, respectively. Our results demonstrate both maternal and developmental toxicity of PFOS in the rat and mouse.	●	●		●	●		●		●	-	1	A	A
1221	実験動物（生殖発生毒性）	Tucker, Deirdre K; Macon, Madisa B; Strynar, Mark J; Dagnino, Sonia; Andersen, Erik; Fenton, Suzanne E	The mammary gland is a sensitive pubertal target in CD-1 and C57Bl/6 mice following perinatal perfluorooctanoic acid (PFOA) exposure	2015	Reprod Toxicol. 2015 Jul;54:26-36. doi: 10.1016/j.reprotox.2014.12.002. Epub 2014 Dec 12.	Perfluorooctanoic acid (PFOA) is a developmental toxicant in mice, with varied strain outcomes depending on dose and period of exposure. The impact of PFOA on female mouse pubertal development at low doses (≤ 1mg/kg) has yet to be determined. Therefore, female offspring from CD-1 and C57Bl/6 dams exposed to PFOA, creating serum concentrations similar to humans, were examined for pubertal onset, including mammary gland development. Pups demonstrated a shorter PFOA elimination half-life than that reported for adult mice. Prenatal exposure to PFOA caused significant mammary developmental delays in female offspring in both strains. Delays started during puberty and persisted into young adulthood; severity was dose-dependent. Also an evaluation of female serum hormone levels and pubertal timing onset revealed no effects of PFOA compared to controls in either strain. These data suggest that the mammary gland is more sensitive to early low level PFOA exposures compared to other pubertal endpoints, regardless of strain.	●	●	●	●	●	●				-		C	C
1222	実験動物（生殖発生毒性）	van Esterik, J C J; Bastos Sales, L; Dollé, M E T; Hå kansson, H; Herlin, M; Legler, J; van der Ven, L T M	Programming of metabolic effects in C57BL/6JxFVB mice by in utero and lactational exposure to perfluorooctanoic acid	2016	Arch Toxicol. 2016 Mar;90(3):701-15. doi: 10.1007/s00204-015-1488-7. Epub 2015 Apr 1.	Perfluorooctanoic acid (PFOA) is known to cause developmental toxicity and is a suggested endocrine disrupting compound (EDC). Early life exposure to EDCs has been implicated in programming of the developing organism for chronic diseases later in life. Here we study perinatal metabolic programming by PFOA using an experimental design relevant for human exposure. C57BL/6JxFVB hybrid mice were exposed during gestation and lactation via maternal feed to seven low doses of PFOA at and below the NOAEL used for current risk assessment (3-3000 μg/kg body weight/day). After weaning, offspring were followed for 23-25 weeks without further exposure. Offspring showed a dose-dependent decrease in body weight from postnatal day 4 to adulthood. Growth under high fat diet in the last 4-6 weeks of follow-up was increased in male and decreased in female offspring. Both sexes showed increased liver weights, hepatic foci of cellular alterations and nuclear dysmorphology. In females, reductions in perigonadal and perirenal fat pad weights, serum triglycerides and cholesterol were also observed. Endocrine parameters, such as glucose tolerance, serum insulin and leptin, were not affected. In conclusion, our study with perinatal exposure to PFOA in mice produced metabolic effects in adult offspring. This is most likely due to disrupted programming of metabolic homeostasis, but the assayed endpoints did not provide a mechanistic explanation. The BMDL of the programming effects in our study is below the current point of departure used for calculation of the tolerable daily intake.	●	●	●							-		B	B
1223	実験動物（生殖発生毒性）	Wan, H. T.; Zhao, Y. G.; Leung, P. Y.; Wong, C. K.	Perinatal exposure to perfluorooctane sulfonate affects glucose metabolism in adult offspring	2014	PLoS ONE. 2014 Jan 31;9(1):e87137. doi: 10.1371/journal.pone.0087137. eCollection 2014.	Perfluoroalkyl acids (PFAAs) are globally present in the environment and are widely distributed in human populations and wildlife. The chemicals are ubiquitous in human body fluids and have a long serum elimination half-life. The notorious member of PFAAs, perfluorooctane sulfonate (PFOS) is prioritized as a global concerning chemical at the Stockholm Convention in 2009, due to its harmful effects in mammals and aquatic organisms. PFOS is known to affect lipid metabolism in adults and was found to be able to cross human placenta. However the effects of in utero exposure to the susceptibility of metabolic disorders in offspring have not yet been elucidated. In this study, pregnant CD-1 mice (F0) were fed with 0, 0.3 or 3 mg PFOS/kg body weight/day in corn oil by oral gavage daily throughout gestational and lactation periods. We investigated the immediate effects of perinatal exposure to PFOS on glucose metabolism in both maternal and offspring after weaning (PND 21). To determine if the perinatal exposure predisposes the risk for metabolic disorder to the offspring, weaned animals without further PFOS exposure, were fed with either standard or high-fat diet until PND 63 Fasting glucose and insulin levels were measured while HOMA-IR index and glucose AUCs were reported. Our data illustrated the first time the effects of the environmental equivalent dose of PFOS exposure on the disturbance of glucose metabolism in F1 pups and F1 adults at PND 21 and 63, respectively. Although the biological effects of PFOS on the elevated levels of fasting serum glucose and insulin levels were observed in both pups and adults of F1, the phenotypes of insulin resistance and glucose intolerance were only evident in the F1 adults. The effects were exacerbated under HFD, highlighting the synergistic action at postnatal growth on the development of metabolic disorders.	●	●	●	●						-		B	B
1224	実験動物（生殖発生毒性）	Wang, Y.; Liu, W.; Zhang, Q.; Zhao, H.; Quan, X.	Effects of developmental perfluorooctane sulfonate exposure on spatial learning and memory ability of rats and mechanism associated with synaptic plasticity	2015	Food Chem Toxicol. 2015 Feb;76:70-6. doi: 10.1016/j.fct.2014.12.008. Epub 2014 Dec 15.	The present study aims to explore the effects of perfluorooctane sulfonate (PFOS) on cognitive function in developing rats and the underlying mechanism associated with synaptic plasticity. Pregnant Wistar rats were fed with 0, 5, and 15 mg/L of PFOS via drinking water during gestation and lactation. Offspring were exposed to PFOS on prenatal and/or postnatal days by cross-fostering. Spatial learning and memory abilities were tested from postnatal day (PND) 35 We also analyzed the expression pattern of the synaptic plasticity-related genes and proteins in the hippocampus on PND7 and PND35. Results revealed that PFOS exposure reduced the spatial learning and memory abilities of the offspring, particularly of those with prenatal exposure. Meanwhile, protein levels of growth-associated protein-43, neural cell adhesion molecule 1, nerve growth factor, and brain-derived neurotrophic factor decreased on PND35, which are involved in the formation of synaptic plasticity. In contrast, significant increase in gap-43, ncam1, and bdnf genes on the mRNA level was observed on PND7, possibly due to the post-transcriptional mechanism. Results of both behavioral effects and molecular endpoints suggested the high risk of prenatal PFOS exposure. The decline of spatial learning and memory abilities induced by developmental PFOS exposure was closely related to synaptic plasticity.	●	●		●					●	-	1	**B**	A
1225	実験動物（生殖発生毒性）	White, S. S.; Kato, K.; Jia, L. T.; Basden, B. J.; Calafat, A. M.; Hines, E. P.; Stanko, J. P.; Wolf, C. J.; Abbott, B. D.; Fenton, S. E.	Effects of perfluorooctanoic acid on mouse mammary gland development and differentiation resulting from cross-foster and restricted gestational exposures	2009	Reprod Toxicol. 2009 Jun;27(3-4):289-298. doi: 10.1016/j.reprotox.2008.11.054. Epub 2008 Nov 27.	The adverse consequences of developmental exposures to perfluorooctanoic acid (PFOA) are established in mice, and include impaired development of the mammary gland (MG). However, the relationships between timing or route of exposure, and consequences in theMGhave not been characterized. To address the effects of these variables on the onset and persistence of MG effects in female offspring, timed pregnant CD-1 dams received PFOA by oral gavage over various gestational durations. Cross-fostering studies	●	●	●	●		●	●		●	-		C	C
1226	実験動物（生殖発生毒性）	White, S. S.; Stanko, J. P.; Kato, K.; Calafat, A. M.; Hines, E. P.; Fenton, S. E.	Gestational and chronic low-dose PFOA exposures and mammary gland growth and differentiation in three generations of CD-1 mice	2011	Environ Health Perspect. 2011 Aug;119(8):1070-6. doi: 10.1289/ehp.1002741. Epub 2011 Apr 18.	BACKGROUND: Prenatal exposure to perfluorooctanoic acid (PFOA), a ubiquitous industrial surfactant, has been reported to delay mammary gland development in female mouse offspring (F1) and the treated lactating dam (P0) after gestational treatments at 3 and 5 mg PFOA/kg/day.OBJECTIVE: We investigated the consequences of gestational and chronic PFOA exposure on F1 lactational function and subsequent development of F2 offspring.METHODS: We treated P0 dams with 0, 1, or 5 mg PFOA/kg/day on gestation days 1-17. In addition, a second group of P0 dams treated with 0 or 1 mg/kg/day during gestation and their F1 and F2 offspring received continuous PFOA exposure (5 ppb) in drinking water. Resulting adult F1 females were bred to generate F2 offspring, whose development was monitored over postnatal days (PNDs) 1-63. F1 gland function was assessed on PND10 by timed-lactation experiments. Mammary tissue was isolated from P0, F1, and F2 females throughout the study and histologically assessed for age-appropriate development.RESULTS: PFOA-exposed F1 dams exhibited diminished lactational morphology, although F1 maternal behavior and F2 offspring body weights were not significantly affected by P0 treatment. In addition to reduced gland development in F1 females under all exposures, F2 females with chronic low-dose drinking-water exposures exhibited visibly slowed mammary gland differentiation from weaning onward. F2 females derived from 5 mg/kg PFOA-treated P0 dams displayed gland morphology similar to F2 chronic water exposure groups on PNDs 22-63.CONCLUSIONS: Gestational PFOA exposure induced delays in mammary gland development and/or lactational differentiation across three generations. Chronic, low-dose PFOA exposure in drinking water was also sufficient to alter mammary morphological development in mice, at concentrations approximating those found in contaminated human water supplies.	●	●	●	●		●	●		●	-		C	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1227	実験動物（生殖発生毒性）	Wolf, Cynthia J; Fenton, Suzanne E; Schmid, Judith E; Calafat, Antonia M; Kuklenyik, Zsuzsanna; Bryant, Xavier A; Thibodeaux, Julie; Das, Kaberi P; White, Sally S; Lau, Christopher S; Abbott, Barbara D	Developmental toxicity of perfluorooctanoic acid in the CD-1 mouse after cross-foster and restricted gestational exposures	2007	Toxicol Sci. 2007 Feb;95(2):462-73. doi: 10.1093/toxsci/kfl159. Epub 2006 Nov 10.	Perfluorooctanoic acid (PFOA) is a persistent pollutant and is detectable in human serum (5 ng/ml in the general population of the Unites States). PFOA is used in the production of fluoropolymers which have applications in the manufacture of a variety of industrial and commercial products (e.g., textiles, house wares, electronics). PFOA is developmentally toxic and in mice affects growth, development, and viability of offspring. This study segregates the contributions of gestational and lactational exposures and considers the impact of restricting exposure to specific gestational periods. Pregnant CD-1 mice were dosed on gestation days (GD) 1-17 with 0, 3, or 5 mg PFOA/kg body weight, and pups were fostered at birth to give seven treatment groups: unexposed controls, pups exposed in utero (3U and 5U), lactationally (3L and 5L), or in utero + lactationally (3U + L and 5U + L). In the restricted exposure (RE) study, pregnant mice received 5 mg PFOA/kg from GD7-17, 10-17, 13-17, or 15-17 or 20 mg on GD15-17. In all PFOA-treated groups, dam weight gain, number of implantations, and live litter size were not adversely affected and relative liver weight increased. Treatment with 5 mg/kg on GD1-17 increased the incidence of whole litter loss and pups in surviving litters had reduced birth weights, but effects on pup survival from birth to weaning were only affected in 5U + L litters. In utero exposure (5U), in the absence of lactational exposure, was sufficient to produce postnatal body weight deficits and developmental delay in the pups. In the RE study, birth weight and survival were reduced by 20 mg/kg on GD15-17. Birth weight was also reduced by 5 mg/kg on GD7-17 and 10-17. Although all PFOA-exposed pups had deficits in postnatal weight gain, only those exposed on GD7-17 and 10-17 also showed developmental delay in eye opening and hair growth. In conclusion, the postnatal developmental effects of PFOA are due to gestational exposure. Exposure earlier in gestation produced stronger responses, but further study is needed to determine if this is a function of higher total dose or if there is a developmentally sensitive period.	●	●		●		●	●			-	1	B	A
1228	実験動物（生殖発生毒性）	Yahia, Doha; El-Nasser, Mahmoud Abd; Abedel-Latif, Manal; Tsukuba, Chiaki; Yoshida, Midori; Sato, Itaru; Tsuda, Shuji	Effects of perfluorooctanoic acid (PFOA) exposure to pregnant mice on reproduction	2010	J Toxicol Sci. 2010 Aug;35(4):527-33. doi: 10.2131/jts.35.527.	Perfluorooctanoic acid (PFOA) has similar characteristics to perfluorooctane sulfonate (PFOS) in reproduction toxicity featured by neonatal death. We found that PFOS exposure to mice during pregnancy led to intracranial blood vessel dilatation of fetuses accompanied by severe lung collapse which caused neonatal mortality. Thus, we adopted the corresponding experimental design to PFOS in order to characterize the neonatal death by PFOA. Pregnant ICR mice were given 1, 5 and 10 mg/kg PFOA daily by gavage from gestational day (GD) 0 to 17 and 18 for prenatal and postnatal evaluations, respectively. Five to nine dams per group were sacrificed on GD 18 for prenatal evaluation; other 10 dams were left to give birth. No maternal death was observed. The liver weight increased dose-dependently, with hepatocellular hypertrophy, necrosis, increased mitosis and mild calcification at 10 mg/kg. PFOA at 10 mg/kg increased serum enzyme activities (GGT, ALT, AST and ALP) with hypoproteinemia and hypolipidemia. PFOA treatment reduced the fetal body weight at 5 and 10 mg/kg. Teratological evaluation showed delayed ossification of the sternum and phalanges and delayed eruption of incisors at 10 mg/kg, but did not show intracranial blood vessel dilatation. Postnatal evaluation revealed that PFOA reduced the neonatal survival rate at 5 and 10 mg/kg. At 5 mg/kg pups were born alive and active and 16% died within 4 days observation, while all died within 6 hr after birth at 10 mg/kg without showing intracranial blood vessel dilatation. The cause of neonatal death by PFOA may be different from PFOS.	●	●	●	●					●	-	1	A	A
1229	実験動物（生殖発生毒性）	Yahia, D.; Tsukuba, C.; Yoshida, M.; Sato, I.; Tsuda, S.	Neonatal death of mice treated with perfluorooctane sulfonate	2008	J Toxicol Sci. 2008 May;33(2):219-26. doi: 10.2131/jts.33.219.	Pregnant mice exposure to perfluorooctane sulfonate (PFOS) causes neonatal death. Ten pregnant ICR mice per group were given 1, 10 or 20 mg/kg PFOS daily by gavage from gestational day (GD) 0 to the end of the study. Five dams per group were sacrificed on GD 18 for prenatal evaluation, the others were left to give birth. Additional studies were conducted for histopathological examination of lungs and heads of fetuses and neonates at birth. PFOS treatment (20 mg/kg) reduced the maternal weight gain and feed intake but increased the water intake. The liver weight increased in a dose-dependent manner accompanied by hepatic hypertrophy at 20 mg/kg. PFOS reduced the fetal body weight in a dose-dependent manner and caused a bilateral enlargement in the neck region in all fetuses at 20 mg/kg and mild enlargement in some fetuses at 10 mg/kg, in addition to skeletal malformations. Almost all fetuses at 20 mg/kg were alive on GD18 and showed normal lung structure; but at parturition, all neonates were inactive and weak, showed severe lung atelectasis and severe dilatation of intracranial blood vessel, and died within a few hours. At 10 mg/kg, all neonates were born alive, 0.27 showed slight lung atelectasis, all of them had mild to severe dilatation of the intracranial blood vessel, and 0.45 of neonates died within 24 hr. The cause of neonatal death in mice exposed to PFOS may be attributed either to the intracranial blood vessel dilatation or to respiratory dysfunction. The former might be a cause of the latter.	●	●	●	●					●	-	1	A	A
1230	実験動物（生殖発生毒性）	Yan, Shengmin; Wang, Jianshe; Zhang, Wei; Dai, Jiayin	Circulating MicroRNA Profiles Altered in Mice after 28 Days Exposure to Perfluorooctanoic Acid	2014	Toxicol Lett. 2014 Jan 3;224(1):24-31. doi: 10.1016/j.toxlet.2013.10.017.	Perfluorooctanoic acid (PFOA) is a stable man-made compound with many industrial and commercial uses. Recently, however, concern has been raised that it may induce various toxicological effects such as hepatotoxicity, immunotoxicity, and developmental toxicity. Because levels of circulating microRNAs (miRNAs) can be altered in several clinical diseases, they may serve as potential novel biomarkers. Here,we explored differences in the profiles of circulating miRNAs in mice after PFOA exposure. Using TaqMan miRNA arrays, we determined that the levels of 24 circulating miRNAs were altered in mice dosed with PFOA at 1.25 mg/kg/d and 73 were altered in mice dosed with 5 mg/kg/d. Eight miRNAs were further validated using TaqMan Real-Time PCR assays. Results were consistent with those obtained from the TaqMan miRNA arrays, except for miR-199a-3p. The most remarkable of the circulating miRNAs (miR-26b-5p and miR-199a-3p) were also up-regulated in the serum of occupational workers in our previous epidemiological study. We also found similar patterns in mice exposed to PFOS. These results demon-strated that circulating miRNA profiles were altered after exposure to high concentrations of PFOA and miR-28-5p, miR-32-5p, miR-122-5p, miR-192-5p, and miR-26b-5p in serum may be linked to effects of PFOA, especially in occupationally exposed people.	●	●								-		C	C
1231	実験動物（生殖発生毒性）	Yang, C.; Tan, Y. S.; Harkema, J. R.; Haslam, S. Z.	Differential effects of peripubertal exposure to perfluorooctanoic acid on mammary gland development in C57Bl/6 and Balb/c mouse strains	2009	Reprod Toxicol. 27: 299-306. doi: 10.1016/j.reprotox.2008.10.003. Epub 2008 Nov 1.	Perfluorooctanoic acid (PFOA), a common and persistent industrial byproduct detected in human sera, has raised health concerns. PFOA is detrimental to lactational function and postnatal mammary gland development in CD-1 mice after gestational exposure. We have examined the peripubertal period (21 through 50 days of age) as an important window of mammary gland susceptibility to environmental exposures that may affect breast cancer risk later in life. The effects of PFOA (0.1-10mg/kg BW) were examined in Balb/c and C57BL/6 mice. PFOA treatment caused hepatocellular hypertrophy and delayed vaginal opening in both mouse strains. While Balb/c mice exhibited only inhibition of mammary gland and uterine development (5, 10mg/kg), C57BL/6 mice exhibited stimulatory effects in both organs at low dose (5mg/kg) and inhibition at higher dose (10mg/kg). This underscores the need for caution when drawing conclusions about the effects of PFOA and possibly other environmental pollutants on the basis of studies in a single mouse strain.	●	●	●	●		●			●	-		B	B
1232	MOA（発生毒性）	Ye, L.; Zhao, B.; Yuan, K.; Chu, Y.; Li, C.; Zhao, C.; Lian, Q. Q.; Ge, R. S.	Gene expression profiling in fetal rat lung during gestational perfluorooctane sulfonate exposure	2014	Toxicol Lett. 209: 270-276. doi: 10.1016/j.toxlet.2011.12.013. Epub 2012 Jan 2.	Perfluorooctane sulfonate (PFOS) is a persistent environmental contaminant found in the tissues of humans and wildlife. It has been reported that gestational exposure to PFOS causes neonatal death of rats. However, the mechanism is still unclear. In this study, we investigated the effects of gestational PFOS exposure on the gene expression profiling of fetal rat lung at pseudoglandular stage. Adult Sprague Dawley dams were dosed orally from gestational day 44913 with 0 (control), 5 mg/kg/day or 20 mg/kg/day PFOS. Animals were euthanized on day 18.5, fetal lung samples were collected for histochemical staining and RNA profiling analysis. PFOS did not cause apparent microscopic changes of fetal lungs. Gene expression profiling revealed that PFOS dose-dependently up-regulated the expression of 21 (5 mg/kg) and 43 (20 mg/kg) genes. These genes include five PPARα target genes (Acot1, Hmgcs2, Fabp4, Fabp1 and Myh7), and 4 of them are involved in lipid metabolism. The other genes were primarily included in the categories of cytoskeletal structure (Tpm1, Tnnt2, Actn3, Myoz2, Tmod1, and Mfap5), extracellular matrix (Ckm, Lum, Tnnc1, Art3, Dcn, Col17a1, Aspn, Ctsk, Itm2a, Spock2 and Orm1), transporting (Cox8h, Cox6a2 and Scnn1a) and secreted proteins (Scgb3a1, Nppb and Spp1). Our study demonstrates that in utero PFOS exposure resulted in the alteration of a set of genes which are involved in significant cytoskeletal, extracellular matrix remodeling, lipid metabolism and secreted proteins in the fetal rat lung.	●	●								-		C	C
1233	実験動物（生殖発生毒性）	York, Raymond G; Kennedy, Gerald L Jr; Olsen, Geary W; Butenhoff, John L	Male reproductive system parameters in a two-generation reproduction study of ammonium perfluorooctanoate in rats and human relevance	2010	Toxicology. 2010 Apr 30;271(1-2):64-72. doi: 10.1016/j.tox.2010.03.005. Epub 2010 Mar 17.	Ammonium perfluorooctanoate (ammonium PFOA) is an industrial surfactant that has been used primarily as a processing aid in the manufacture of fluoropolymers. The environmental and metabolic stability of PFOA together with its presence in human blood and long elimination half-life have led to extensive toxicological studies in laboratory animals. Two recent publications based on observations from the Danish general population have reported: (1) a negative association between serum concentrations of PFOA in young adult males and their sperm counts and (2) a positive association among women with time to pregnancy. A two-generation reproduction study in rats was previously published (2004) in which no effects on functional reproduction were observed at doses up to 30mg ammonium PFOA/kg body weight. The article contained the simple statement: "In males, fertility was normal as were all sperm parameters". In order to place the recent human epidemiological data in perspective, herein we provide the detailed male reproductive parameters from that study, including sperm quality and testicular histopathology. Sperm parameters in rats from the two-generation study in all ammonium PFOA treatment groups were unaffected by treatment with ammonium PFOA. These observations reflected the normal fertility observations in these males. No evidence of altered testicular and sperm structure and function was observed in ammonium PFOA-treated rats whose mean group serum PFOA concentrations ranged up to approximately 50,000ng/mL. Given that median serum PFOA in the Danish cohorts was approximately 5ng/mL, it seems unlikely that concentrations observed in the general population, including those recently reported in Danish general population, could be associated causally with a real decrement in sperm number and quality.	●	●				●				-		C	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ラン①	文献ラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1234	実験動物（生殖発生毒性）	Zhang, D.,eY; Xu, X. L.,u; Ruan, Q.,in; Shen, X.,iuY; Lu, Y.,in	Subchronic Effects of Perfluorooctane Sulphonate on the Testicular Morphology and Spermatogenesis in Mice	2019	Pakistan J Zool. 51: 2217-2223. doi: 10.17582/journal.pjz/2019.51.6.2217.2223	To determine the subchronic male reproductive toxicity of PFOS, male mice were administrated with a serial dosage of PFOS for 90 days for testicular observation and spermatogenesis evaluation. PFOS >= 11 mg/kg (accumulative dosage) resulted in visible histopathological changing in testis, including disorder and vacuolization of spermatogenic cells. Changed testicular organ coefficient (for dosage >= 55 mg/kg), decreased sperm concentration (for 110 mg/kg dosage), decreased motility (for 110 mg/kg dosage) and increased sperm malformation (for all of the treated groups) were also confirmed (p<0.05). Sperm malformation showed high sensitivity to PFOS exposure. A sperm malformation percentage, varying from 0.11 to 51.20%, was confirmed for the treated groups. As to various sperm malformation types, curved body type constituted the most proportion. The treated groups showed a curved body malformation percentage varied from 0.08 to 43.5%, due to different PFOS dosage. The observations indicate that subchronic exposure of PFOS can interfere with spermatogenesis process and affect sperm quality in mammals.	●	●							-		C	C
1235	実験動物（生殖発生毒性）	Zhang, H.; Lu, H.; Chen, P.; Chen, X.; Sun, C.; Ge, R. S.; Su, Z.; Ye, L.	Effects of gestational Perfluorooctane Sulfonate exposure on the developments of fetal and adult Leydig cells in F1 males	2020	Environ Pollut. 262: 114241. doi: 10.1016/j.envpol.2020.114241. Epub 2020 Feb 21.	Studies have showed that some of the most common male reproductive disorders present in adult life might have a fetal origin. Perfluorooctane sulfonic (PFOS) is one of the major environmental pollutants that may affect the development of male reproductive system if exposed during fetal or pubertal periods. However, whether PFOS exposure during fetal period affects testicular functions in the adult is still unclear. Herein, we investigated the effects of a brief gestational exposure to PFOS on the development of adult Leydig- and Sertoli-cells in the male offspring. Eighteen pregnant Sprague-Dawley rats were randomly divided into three groups and each received 0, 1 or 5 mg/kg/day PFOS from gestational day 5-20. The testicular functions of F1 males were evaluated on day 1, 35 and 90 after birth. PFOS treatment significantly decreased serum testosterone levels of animals by all three ages examined. The expression level of multiple mRNAs and proteins of Leydig (Scarb1, Cyp11a1, Cyp17a1 and Hsd17b3) and Sertoli (Dhh and Sox9) cells were also down-regulated by day 1 and 90 PFOS exposure might also inhibit Leydig cell proliferation since the number of PCNA-positive Leydig cells were significantly reduced by postnatal day 35 Accompanied by changes in Leydig cell proliferation and differentiation, PFOS also significantly reduced phosphorylation of glycogen synthase kinase-3β while increased phosphorylation of β-catenin. In conclusion, gestational PFOS exposure may have significant long-term effects on adult testicular functions of the F1 offspring. Changes in Wnt signaling may play a role in the process.	●	●							-		B	B
1236	実験動物（生殖発生毒性）	Zhang, H.; Lu, Y.; Luo, B.; Yan, S.; Guo, X.; Dai, J.	Proteomic analysis of mouse testis reveals perfluorooctanoic acid-induced reproductive dysfunction via direct disturbance of testicular steroidogenic machinery	2014	J Proteome Res. 13: 3370-3385. doi: 10.1021/pr500228d. Epub 2014 Jun 25.	Perfluorooctanoic acid (PFOA) is a ubiquitous environmental pollutant suspected of being an endocrine disruptor; however, mechanisms of male reproductive disorders induced by PFOA are poorly understood. In this study, male mice were exposed to 0, 0.31, 1.25, 5, and 20 mg PFOA/kg/day by oral gavage for 28 days. PFOA significantly damaged the seminiferous tubules and reduced testosterone and progesterone levels in the testis in a dose-dependent manner. Furthermore, PFOA exposure reduced sperm quality. We identified 93 differentially expressed proteins between the control and the 5 mg/kg/d PFOA treated mice using a quantitative proteomic approach. Among them, insulin like-factor 3 (INSL3) and cytochrome P450 cholesterol side-chain cleavage enzyme (CYP11A1) as Leydig-cell-specific markers were significantly decreased. We examined in detail the expression patterns of CYP11A1 and associated genes involved in steroidogenesis in the mouse testis. PFOA inhibited the mRNA and protein levels of CYP11A1 and the mRNA levels of 17β-hydroxysteroid dehydrogenase (17β-HSD) in a dose-dependent manner. Moreover, in vitro study showed the reduction in progesterone levels was accompanied by decreased expression of CYP11A1 in cAMP-stimulated mLTC-1 cells. Our findings indicate that PFOA exposure can impair male reproductive function, possibly by disturbing testosterone levels, and CPY11A1 may be a major steroidogenic enzyme targeted by PFOA.	●	●	●						●	-		C	C
1237	実験動物（生殖発生毒性）	Zhang, Y.; Cao, X.; Chen, L.; Qin, Y.; Xu, Y.; Tian, Y.; Chen, L.	Exposure of female mice to perfluorooctanoic acid suppresses hypothalamic kisspeptin-reproductive endocrine system through enhanced hepatic fibroblast growth factor 21 synthesis, leading to ovulation failure and prolonged dioestrus	2020	J Neuroendocrinol. 2020 May;32(5):e12848. doi: 10.1111/jne.12848. Epub 2020 Apr 19.	Perfluorooctanoic acid (PFOA) is widely used in household applications. High-dose exposure to PFOA has been associated with increased risks of infertility and premature ovarian insufficiency in woman. PFOA can alter hepatic gene expression by activating peroxisome proliferator-activated receptor α (PPARα). The present study investigated whether exposure to PFOA via PPARα activation alters the synthesis of hepatic fibroblast growth factor 21 (FGF21) to disturb female neuroendocrine and reproductive function. In the present study, we show that the oral administration of PFOA (2 or 5 mg kg-1) in adult female mice (PFOA mice) caused prolonged dioestrous, a reduction in the number of corpora lutea and decreased levels of hypothalamic gonadotrophin-releasing hormone, serum progesterone and luteinising hormone (LH). Exposure to PFOA decreased the expression of vasopressin in the suprachiasmatic nucleus (SCN) and kisspeptin in the anteroventral periventricular nucleus (AVPV) with deficits in preovulation or oestrogen-induced LH surge. PFOA via activation of PPARα increased dose-dependently hepatic FGF21 expression, leading to elevated serum and hypothalamic FGF21 concentrations. Treatment of PFOA mice with the PPARα antagonist GW6471 or the FGF21 inhibitor PD173074 rescued SCN vasopressin and AVPV-kisspeptin expression. Either administration of GW6471 and PD173074 or treatment with vasopressin and the G protein coupled receptor 54 agonist kisspeptin-10 in PFOA-mice was able to recover the regular oestrous cycle, ovulation ability, LH surge production and reproductive hormone levels. The present study provides in vivo evidence that exposure to PFOA (≥2 mg kg-1) in mice causes down-regulation of the kisspeptin-reproductive endocrine system by enhancing PPARα-mediated hepatic FGF21 expression. The liver-brain reproductive endocrine disorder caused by PFOA exposure may lead to prolonged dioestrous and ovulation failure.	●	●							-		C	C
1238	実験動物（生殖発生毒性）	Zhong, S. Q.; Chen, Z. X.; Kong, M. L.; Xie, Y. Q.; Zhou, Y.; Qin, X. D.; Paul, G.; Zeng, X. W.; Dong, G. H.	Testosterone-Mediated Endocrine Function and TH1/TH2 Cytokine Balance after Prenatal Exposure to Perfluorooctane Sulfonate: By Sex Status	2016	Int J Mol Sci. 2016 Sep 12;17(9):1509. doi: 10.3390/ijms17091509.	Little information exists about the evaluation of potential developmental immunotoxicity induced by perfluorooctane sulfonate (PFOS), a synthetic persistent and increasingly ubiquitous environmental contaminant. To assess potential sex-specific impacts of PFOS on immunological health in the offspring, using male and female C57BL/6 mice, pups were evaluated for developmental immunotoxic effects after maternal oral exposure to PFOS (0.1, 1 and 5 mg PFOS/kg/day) during Gestational Days 1-17. Spontaneous TH1/TH2-type cytokines, serum levels of testosterone and estradiol were evaluated in F1 pups at four and eight weeks of age. The study showed that male pups were more sensitive to the effects of PFOS than female pups. At eight weeks of age, an imbalance in TH1/TH2-type cytokines with excess TH2 cytokines (IL-4) was found only in male pups. As for hormone levels, PFOS treatment in utero significantly decreased serum testosterone levels and increased estradiol levels only in male pups, and a significant interaction between sex and PFOS was observed for serum testosterone at both four weeks of age (pinteraction = 0.0049) and eight weeks of age (pinteraction = 0.0227) and for estradiol alternation at four weeks of age (pinteraction = 0.0351). In conclusion, testosterone-mediated endocrine function may be partially involved in the TH1/TH2 imbalance induced by PFOS, and these deficits are detectable among both young and adult mice and may affect males more than females.	●	●							-		C	C
1239	実験動物（生殖発生毒性）	Zirkin, Barry R; Papadopoulos, Vassilios	Leydig cells: formation, function, and regulation	2018	Biol Reprod. 2018 Jul 1;99(1):101-111. doi: 10.1093/biolre/ioy059.	Herein we summarize important discoveries made over many years about Leydig cell function and regulation. Fetal Leydig cells produce the high levels of androgen (testosterone or androstenedione, depending upon the species) required for differentiation of male genitalia and brain masculinization. Androgen production declines with loss of these cells, reaching a nadir at postpartum. Testosterone then gradually increases to high levels with adult Leydig cell development from stem cells. In the adult, luteinizing hormone (LH) binding to Leydig cell LH receptors stimulates cAMP production, increasing the rate of cholesterol translocation into the mitochondria. Cholesterol is metabolized to pregnenolone by the CYP11A1 enzyme at the inner mitochondrial membrane, and pregnenolone to testosterone by mitochondria and smooth endoplasmic reticulum enzymes. Cholesterol translocation to the inner mitochondrial membrane is mediated by a protein complex formed at mitochondrial contact sites that consists of the cholesterol binding translocator protein, voltage dependent anion channel, and other mitochondrial and cytosolic proteins. Steroidogenic acute regulatory protein acts at this complex to enhance cholesterol movement across the membranes and thus increase testosterone formation. The 14-3-3γ and ε adaptor proteins serve as negative regulators of steroidogenesis, controlling the maximal amount of steroid formed. Decline in testosterone production occurs in many aging and young men, resulting in metabolic and quality-of-life changes. Testosterone replacement therapy is widely used to elevate serum testosterone levels in hypogonadal men. With knowledge gained of the mechanisms involved in testosterone formation, it is also conceivable to use pharmacological means to increase serum testosterone by Leydig cell stimulation.	●	●							-		C	C
1240	実験動物（生殖発生毒性）	Abbott, Barbara D; Wolf, Cynthia J; Das, Kaberi P; Zehr, Robert D; Schmid, Judith E; Lindstrom, Andrew B; Strynar, Mark J; Lau, Christopher	Developmental toxicity of perfluorooctane sulfonate (PFOS) is not dependent on expression of peroxisome proliferator activated receptor-alpha (PPARa) in the mouse.	2009	Reprod Toxicol. 2009 Jun;27(3-4):258-265. doi: 10.1016/j.reprotox.2008.05.061. Epub 2008 May 24.	Perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) are members of a family of perfluorinated compounds. Both are environmentally persistent and found in the serum of wildlife and humans. PFOS and PFOA are developmentally toxic in laboratory rodents. Exposure to these chemicals in utero delays development and reduces postnatal survival and growth. Exposure to PFOS on the last 4 days of gestation in the rat is sufficient to reduce neonatal survival. PFOS and PFOA are weak agonists of peroxisome proliferator activated receptor-alpha (PPAR alpha). The reduced postnatal survival of neonatal mice exposed to PFOA was recently shown to depend on expression of PPAR alpha. This study used PPAR alpha knockout (KO) and 129S1/SvlmJ wild type (WT) mice to determine if PPAR alpha expression is required for the developmental toxicity of PFOS. After mating overnight, the next day was designated gestation day (GD) 0. WT females were weighed and dosed orally from GD15 to 18 with 0.5% Tween-20, 4.5, 6.5, 8.5, or 10.5mg PFOS/kg/day. KO females were dosed with 0.5% Tween-20, 8.5 or 10.5mg PFOS/kg/day. Dams and pups were observed daily and pups were weighed on postnatal day (PND) 1 and PND15. Eye opening was recorded from PND12 to 15. Dams and pups were killed on PND15, body and liver weights recorded, and serum collected. PFOS did not affect maternal weight gain or body or liver weights of the dams on PND15. Neonatal survival (PND1-15) was significantly reduced by PFOS in both WT and KO litters at all doses. WT and KO pup birth weight and weight gain from PND1 to 15 were not significantly affected by PFOS exposure. Relative liver weight of WT and KO pups was significantly increased by the 10.5mg/kg dose. Eye opening of PFOS-exposed pups was slightly delayed in WT and KO on PND13 or 14, respectively. Because results in WT and KO were comparable, it is concluded that PFOS-induced neonatal lethality and delayed eye opening are not dependent on activation of PPAR alpha.			●	●	●					-		C	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1241	実験動物（生殖発生毒性）	Abbott, Barbara D; Wood, Carmen R; Watkins, Andrew M; Tatum-Gibbs, Katoria; Das, Kaberi P; Lau, Christopher	Effects of perfluorooctanoic acid (PFOA) on expression of peroxisome proliferator-activated receptors (PPAR) and nuclear receptor-regulated genes in fetal and postnatal CD-1 mouse tissues.	2012	Reprod Toxicol. 2012 Jul;33(4):491-505. doi: 10.1016/j.reprotox.2011.11.005. Epub 2011 Dec 1.	PPARs regulate metabolism and can be activated by environmental contaminants such as perfluorooctanoic acid (PFOA). PFOA induces neonatal mortality, developmental delay, and growth deficits in mice. Studies in genetically altered mice showed that PPARα is required for PFOA-induced developmental toxicity. In this study, pregnant CD-1 mice were dosed orally from GD1 to 17 with water or 5mg PFOA/kg to examine PPARα, PPARβ, and PPARγ expression and profile the effects of PFOA on PPAR-regulated genes. Prenatal and postnatal liver, heart, adrenal, kidney, intestine, stomach, lung, spleen, and thymus were collected at various developmental ages. RNA and protein were examined using qPCR and Western blot analysis. PPAR expression varied with age in all tissues, and in liver PPARα and PPARγ expression correlated with nutritional changes as the pups matured. As early as GD14, PFOA affected expression of genes involved in lipid and glucose homeostatic control. The metabolic disruption produced by PFOA may contribute to poor postnatal survival and persistent weight deficits of CD-1 mouse neonates.			●	●					●	-		C	C
1242	実験動物（生殖発生毒性）	Butenhoff, John L; Chang, Shu-Ching; Ehresman, David J; York, Raymond G	Evaluation of potential reproductive and developmental toxicity of potassium perfluorohexanesulfonate in Sprague Dawley rats	2009	Reprod Toxicol. 2009 Jun;27(3-4):331-341. doi: 10.1016/j.reprotox.2009.01.004. Epub 2009 Jan 21.	This study evaluates the potential reproductive and developmental toxicity of perfluorohexanesulfonate (PFHxS), a surfactant found in sera of the general population. In a modified OECD 422 guideline-based design, 15 rats per sex and treatment group (control, 0.3, 1, 3, and 10mg/kg-d) were dosed by gavage with potassium PFHxS (K(+)PFHxS) or vehicle (0.5% carboxymethylcellulose) 14 days prior to cohabitation, during cohabitation, and until the day before sacrifice (21 days of lactation or presumed gestation day 25 (if not pregnant) for females and minimum of 42 days of treatment for males). Offspring were not dosed by gavage but were exposed by placental transfer in utero and potentially exposed via milk. Evaluations were made for reproductive success, clinical signs, body weight, food consumption, estrous cycling, neurobehavioral effects, gross and microscopic anatomy of selected organs, sperm, hematology, clinical pathology, and concentration of PFHxS in serum and liver. Additional three rats per sex per group were added to obtain sera and liver samples for PFHxS concentration determinations during the study. No reproductive or developmental effects were observed. There were no treatment-related effects in dams or offspring. K(+)PFHxS-induced effects noted in parental males included: (1) at all doses, reductions in serum total cholesterol; (2) at 0.3, 3, and 10mg/kg-d, decreased prothrombin time; (3) at 3 and 10mg/kg-d, increased liver-to-body weight and liver-to-brain weight ratios, centrilobular hepatocellular hypertrophy, hyperplasia of thyroid follicular cells, and decreased hematocrit; (4) at 10mg/kg-d, decreased triglycerides and increased albumin, BUN, ALP, Ca(2+), and A/G ratio. Serum and liver concentrations of PFHxS are reported for parents, fetuses, and pups. PFHxS was not a reproductive or developmental toxicant under study conditions.			●	●				●		-		B	B
1243	実験動物（生殖発生毒性）	Case, M T; York, R G; Christian, M S	Rat and rabbit oral developmental toxicology studies with two perfluorinated compounds	2001	Int J Toxicol. 2001 Mar-Apr;20(2):101-9. doi: 10.1080/10915810151115236.	Developmental toxicology (teratology) studies were done on two perfluorinated compounds-perfluorooctanesulfonate (PFOS) and 2-(N-ethylperfluorooctanesulfonamido)ethyl alcohol (N-EtFOSE) in rats and rabbits. Dose selection for these oral developmental toxicity studies were based upon dose-range study results. Dose levels of 0, 1, 5, 10, and 20 mg/kg/day were used for the rat N-EtFOSE study, and dose levels of 0, 0.1, 1.0, 2.5, and 3.75 mg/kg/day were used for both the PFOS and the N-EtFOSE rabbit studies. Although no compound-related deaths occurred in the dosed pregnant females on the developmental toxicity studies, maternal toxicity (reduced body weight gain and feed consumption) was present at higher dose levels in all three studies. At high maternally toxic doses, associated effects occurred in the conceptuses--increased abortions in PFOS and N-EtFOSE rabbits, reduced fetal weights in N-EtFOSE rats and PFOS rabbits, and increased late resorptions in N-EtFOSE rabbits. Detailed external gross, soft tissue, and skeletal fetal examinations failed to reveal any compound-related malformations in either species. Similar results, that is, only effects associated with maternal toxicity, had been found in previously conducted PFOS rat developmental toxicity studies. It was concluded that these perfluorinated compounds were not selective developmental toxicants in either rats or rabbits.			●	●	●		●		●	-		B	B
1244	実験動物（生殖発生毒性）	Chang, Sue; Butenhoff, John L; Parker, George A; Coder, Prägati S; Zitzow, Jeremiah D; Krisko, Ryan M; Bjork, James A; Wallace, Kendall B; Seed, Jennifer G	Reproductive and developmental toxicity of potassium perfluorohexanesulfonate in CD-1 mice	2018	Reprod Toxicol. 2018 Jun;78:150-168. doi: 10.1016/j.reprotox.2018.04.007. Epub 2018 Apr 22.	Potassium perfluorohexanesulfonate (K(+)PFHxS) was evaluated for reproductive/developmental toxicity in CD-1 mice. Up to 3 mg/kg-d K(+)PFHxS was administered (n = 30/sex/group) before mating, for at least 42 days in F(0) males, and for F(0) females, through gestation and lactation. F(1) pups were directly dosed with K(+)PFHxS for 14 days after weaning. There was an equivocal decrease in live litter size at 1 and 3 mg/kg-d, but the pup-born-to-implant ratio was unaffected. Adaptive hepatocellular hypertrophy was observed, and in 3 mg/kg-d F(0) males, it was accompanied by concomitant decreased serum cholesterol and increased alkaline phosphatase. There were no other toxicologically significant findings on reproductive parameters, hematology/clinical pathology/TSH, neurobehavioral effects, or histopathology. There were no treatment-related effects on postnatal survival, development, or onset of preputial separation or vaginal opening in F(1) mice. Consistent with previous studies, our data suggest that the potency of PFHxS is much lower than PFOS in rodents.			●	●						-		B	B
1245	実験動物（生殖発生毒性）	Chen, Yong; Li, Huitao; Mo, Jiaying; Chen, Xiuxiu; Wu, Keyang; Ge, Fei; Ma, Leikai; Li, Xiaoheng; Guo, Xiaoling; Zhao, Junzhao; Ge, Ren-Shan	Perfluorododecanoic acid blocks rat leydig cell development during prepuberty	2019	Chem Res Toxicol. 2019 Jan 22;32(1):146-155. doi: 10.1021/acs.chemrestox.8b00241. Epub 2018 Dec 24.	Perfluorododecanoic acid (PFDoA) has been used as a surfactant and may have reproductive toxicity. However, whether PFDoA influences Leydig cell development during prepuberty remains unknown. In the present study, 21-day-old male Sprague-Dawley rats were gavaged 0, 5, or 10 mg/kg PFDoA from postnatal day 21 to 35. PFDoA decreased the serum concentrations of testosterone, luteinizing hormone, and follicle-stimulating hormone at doses of 5 and 10 mg/kg without influencing Leydig cell number and proliferation. However, PFDoA down-regulated the expression of Leydig cell genes (Lhcgr, Scarb1, Star, Cyp11a1, Cyp17a1, and Hsd11b1) or their proteins. PFDoA dose-dependently reduced SIRT1 and PGC-1α levels. PFDoA did not affect AMPK and AKT2 levels but decreased their phosphorylation. We also treated primary progenitor Leydig cells purified from prepubertal rat testes with PFDoA for 24 h. It in vitro lowered viability and decreased mitochondrial membrane potential of progenitor Leydig cells, but it stimulated the generation of the intracellular reactive oxygen species and induced Leydig cell apoptosis at 10 μM. In conclusion, PFDoA blocks rat Leydig cell development during the prepubertal period possibly via targeting AMPK/SIRT1/PGC-1α and AKT2 signaling pathways.			●							-		C	C
1246	実験動物（生殖発生毒性）	Das, Kaberi P; Grey, Brian E; Zehr, Robert D; Wood, Carmen R; Butenhoff, John L; Chang, Shu-Ching; Ehresman, David J; Tan, Yu-Mei; Lau, Christopher	Effects of perfluorobutyrate exposure during pregnancy in the mouse	2008	Toxicol Sci. 2008 Sep;105(1):173-81. doi: 10.1093/toxsci/kfn099. Epub 2008 May 28.	Perfluorobutyrate (PFBA) is a perfluoroalkyl acid (PFAA) found in the environment. Previous studies have indicated developmental toxicity of PFAAs (perfluorooctane sulfonate [PFOS] and perfluorooctanoate [PFOA]); the current study examines that of PFBA. PFBA/NH4(+) was given to timed-pregnant CD-1 mice by oral gavage daily from gestational day (GD) 1 to 17 at 35, 175, or 350 mg/kg (chosen to approximate the developmentally toxic doses of PFOA); controls received water. At GD 18, serum levels of PFBA were 3.8, 4.4, and 2.5 microg/ml, respectively, in the three treated groups. PFBA did not significantly affect maternal weight gain, number of implantations, fetal viability, fetus weight, or incidence of fetal malformations. Incidence of full-litter loss was significantly greater in the 350 mg/kg group, and maternal liver weights were significantly increased in the 175 and 350 mg/kg groups. In contrast to PFOA and PFOS, PFBA exposure during pregnancy did not adversely affect neonatal survival or postnatal growth. Liver enlargement was detected in the PFBA-exposed pups on postnatal day (PD) 1, but not by PD 10. Expression of selected hepatic genes in PFBA-exposed pups at PD 1 did not reveal any significant changes from controls. A significant delay in eye-opening in offspring was detected in all three PFBA groups, and slight delays in the onset of puberty were noted in the 175 and 350 mg/kg groups. These data suggest that exposure to PFBA during pregnancy in the mouse did not produce developmental toxicity comparable to that observed with PFOA, in part, due to rapid elimination of the chemical.			●	●						-		C	C
1247	実験動物（生殖発生毒性）	Das, Kaberi P; Grey, Brian E; Rosen, Mitchell B; Wood, Carmen R; Tatum-Gibbs, Katoria R; Zehr, R Daniel; Strynar, Mark J; Lindstrom, Andrew B; Lau, Christopher	Developmental toxicity of perfluorononanoic acid in mice	2015	Reprod Toxicol. 2015 Jan;51:133-44. doi: 10.1016/j.reprotox.2014.12.012. Epub 2014 Dec 25.	Perfluorononanoic acid (PFNA) is a ubiquitous and persistent environmental contaminant. Although its levels in the environment and in humans are lower than those of perfluorooctane sulfonate (PFOS) or perfluorooctanoic acid (PFOA), a steady trend of increases in the general population in recent years has drawn considerable interest and concern. Previous studies with PFOS and PFOA have indicated developmental toxicity in laboratory rodent models. The current study extends the evaluation of these adverse outcomes to PFNA in mice. PFNA was given to timed-pregnant CD-1 mice by oral gavage daily on gestational day 1-17 at 1, 3, 5 or 10mg/kg; controls received water vehicle. Dams given 10mg/kg PFNA could not carry their pregnancy successfully and effects of this dose group were not followed. Similar to PFOS and PFOA, PFNA at 5mg/kg or lower doses produced hepatomegaly in the pregnant dams, but did not affect the number of implantations, fetal viability, or fetal weight. Mouse pups were born alive and postnatal survival in the 1 and 3mg/kg PFNA groups was not different from that in controls. In contrast, although most of the pups were also born alive in the 5mg/kg PFNA group, 80% of these neonates died in the first 10 days of life. The pattern of PFNA-induced neonatal death differed somewhat from those elicited by PFOS or PFOA. A majority of the PFNA-exposed pups survived a few days longer after birth than those exposed to PFOS or PFOA, which typically died within the first 2 days of postnatal life. Surviving neonates exposed to PFNA exhibited dose-dependent delays in eye opening and onset of puberty. In addition, increased liver weight seen in PFNA-exposed offspring persisted into adulthood and was likely related to the persistence of the chemical in the tissue. Evaluation of gene expression in fetal and neonatal livers revealed robust activation of peroxisome proliferator-activated receptor-alpha (PPARα) target genes by PFNA that resembled the responses of PFOA. Our results indicate that developmental toxicity of PFNA in mice is comparable to that of PFOS and PFOA, and that these adverse effects are likely common to perfluoroalkyl acids that persist in the body.			●	●						-		C	C
1248	実験動物（生殖発生毒性）	Dixon, Darlene; Reed, Casey E; Moore, Alicia B; Gibbs-Flournoy, Eugene A; Hines, Erin P; Wallace, Elizabeth A; Stanko, Jason P; Lu, Yi; Jefferson, Wendy N; Newbold, Retha R; Fenton, Suzanne E	Histopathologic changes in the uterus, cervix and vagina of immature CD-1 mice exposed to low doses of perfluorooctanoic acid (PFOA) in a uterotrophic assay	2012	Reprod Toxicol. 2012 Jul;33(4):506-512. doi: 10.1016/j.reprotox.2011.10.011. Epub 2011 Nov 28.	The estrogenic and antiestrogenic potential of perfluorooctanoic acid (PFOA) was assessed using an immature mouse uterotrophic assay and by histologic evaluation of the uterus, cervix and vagina following treatment. Female offspring of CD-1 dams were weaned at 18days old and assigned to groups of equal weight, and received 0, 0.01, 0.1, or 1mg PFOA/kg BW/d by gavage with or without 17-β estradiol (E(2), 500μg/kg/d) from PND 18-20 (n=8/treatment/block). At 24h after the third dose (PND 21), uteri were removed and weighed. Absolute and relative uterine weights were significantly increased in the 0.01mg/kg PFOA only group. Characteristic estrogenic changes were present in all E(2)-treated mice; however, they were minimally visible in the 0.01 PFOA only mice. These data suggest that at a low dose PFOA produces minimal histopathologic changes in the reproductive tract of immature female mice, and does not antagonize the histopathologic effects of E(2).			●	●		●			●	-		C	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ランク①	文献ランク②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1249	実験動物（生殖発生毒性）	Era, Saho; Harada, Kouji H; Toyoshima, Megumi; Inoue, Kayoko; Minata, Mutsuko; Saito, Norimitsu; Takigawa, Toshiya; Shiota, Kouhei; Koizumi, Akio	Cleft palate caused by perfluorooctane sulfonate is caused mainly by extrinsic factors	2009	Toxicology. 2009 Feb 4;256(1-2):42-7. doi: 10.1016/j.tox.2008.11.003. Epub 2008 Nov 12.	Perfluorooctane sulfonate (PFOS) is found ubiquitously in the environment, and is known to cause developmental toxicity, including cleft plate (CP). The aim of the present study was to elucidate the mechanism of CP associated with in utero exposure to PFOS in mice. We first examined whether the concentration of PFOS in fetal serum was related to susceptibility to CP. We compared palatogenesis following the administration of various concentrations of PFOS to dams. We conducted histological examination on gestational day (GD) 15 and 18, and alizarin red/alcian blue staining of fetal heads on GD18. Finally, we cultured palatal shelves (PSs) of GD14 fetuses, which had not yet made contact with each other, for 48h, to examine whether the shelves maintained the ability to fuse. The incidence of CP increased from 7.3% with a fetal serum concentration of PFOS of 110.7+/-13.4microg/ml (13mg/kg) to 78.3% with 138.6+/-0.9microg/ml (20mg/kg). PFOS at 50mg/kg on GD11-15 caused CP at a rate of 6.1%, meanwhile PFOS at 20mg/kg on GD1-17 caused a CP rate of 89.3%. Failure of palatal shelf elevation was observed with 20mg/kg PFOS. PFOS at 20mg/kg on GD1-17 and 50mg/kg on GD11-15 inhibited mandibular growth to the same extent, even though the rate of CP was different. Explants exposed to PFOS 20mg/kg and Tween 20 showed 94% (34/36) and 100% (31/31) fusion, respectively. We demonstrated that increasing the oral dose of PFOS from 13 to 20mg/kg resulted in a significant increase in CP even though there was only a small increase in serum concentration of PFOS. PFOS prevented elevation of the PSs above the tongue because their growth/fusion potential was maintained. Mandibular hypoplasia did not seem to play a critical role in the pathogenesis of CP.			●	●	●					-		B	B
1250	実験動物（生殖発生毒性）	Feng, Xuejiao; Cao, Xinyuan; Zhao, Shasha; Wang, Xiaoli; Hua, Xu; Chen, Lin; Chen, Ling	Exposure of pregnant mice to perfluorobutanesulfonate causes hypothyroxinemia and developmental abnormalities in female offspring	2017	Toxicol Sci. 2017 Feb;155(2):409-419. doi: 10.1093/toxsci/kfw219. Epub 2016 Nov 1.	Perfluorobutanesulfonate (PFBS) is widely used in many industrial products. We evaluated the influence of prenatal PFBS exposure on perinatal growth and development, pubertal onset, and reproductive and thyroid endocrine system in female mice. Here, we show that when PFBS (200 and 500 mg/kg/day) was orally administered to pregnant mice (PFBS-dams) on days 1-20 of gestation; their female offspring (PFBS-offspring) exhibited decreased perinatal body weight and delayed eye opening compared with control offspring. Vaginal opening and first estrus were also significantly delayed in PFBS-offspring, and diestrus was prolonged. Ovarian and uterine size, as well as follicle and corpus luteum numbers, were reduced in adult PFBS-offspring. Furthermore, pubertal and adult PFBS-offspring exhibited decreases in serum estrogen (E2) and progesterone (P4) levels with the elevation of luteinizing hormone levels. Notably, decreases in serum total thyroxine (T4) and 3,3', 5-triiodothyronine (T3) levels were observed in fetal, pubertal, and adult PFBS-offspring in conjunction with slight increases in thyroid-stimulating hormone (TSH) and thyrotropin-releasing hormone levels. In addition, PFBS-dams exhibited significant decreases in total T4 and T3 levels and free T4 levels and increases in TSH levels, but no changes in E2 and P4 levels. These results indicate that prenatal PFBS exposure (≥200 mg/kg/day) causes permanent hypothyroxinemia accompanied by deficits in perinatal growth, pubertal onset, and reproductive organ development in female mice.			●	●						-		C	B
1251	実験動物（生殖発生毒性）	Harris, M W; Birnbaum, L S	Developmental toxicity of perfluorodecanoic acid in C57BL/6N mice	1989	Fundam Appl Toxicol. 1989 Apr;12(3):442-8. doi: 10.1016/0272-0590(89)90018-3.	Perfluorodecanoic acid (PFDA) is a representative of the perfluorinated carboxylic acids used as commercial wetting agents and flame retardants. Signs of PFDA toxicity have been reported to resemble those seen after exposure to TCDD. To determine if PFDA exhibits teratogenic effects similar to those of TCDD or is a developmental toxin, time-mated C57BL/6N mice were administered PFDA by gavage in corn oil (10 ml/kg) on gestation days (gd) 10-13 or gd 6-15 at levels of 0, 0.25, 0.5, 1.0, 2.0, 4.0, 8.0, 16.0, or 32.0 mg/kg/day or 0, 0.03, 0.3, 1.0, 3.0, 6.4, or 12.8 mg/kg/day, respectively. Dams were killed on gd 18 and maternal and fetal toxicity was assessed. Fetuses were examined for external, visceral, or skeletal malformations. Maternal body weight gain (corrected for the weight of the gravid uterus) was significantly reduced as a result of PFDA treatment at 6.4 and 12.8 mg/kg/day (gd 6-15) and 16.0 and 32.0 mg/kg/day (gd 10-13). Fetal viability was decreased only in those groups showing extensive maternal body weight loss. Fetal body weights were significantly reduced at levels as low as 0.1 mg/kg/day (gd 6-15) and 0.5 mg/kg/day (gd 10-13). No hydronephrosis, cleft palate, or edema was observed nor were any other soft tissue or skeletal malformations detected. Thus, PFDA does not produce malformations in C57BL/6N mice, and the developmental toxicity observed (increased fetal mortality and decreased live fetal body weight) was seen only at doses that were maternally toxic.			●	●						-		C	C
1252	実験動物（生殖発生毒性）	Harris, M W; Uraih, L C; Birnbaum, L S	Acute toxicity of perfluorodecanoic acid in C57BL/6 mice differs from 2,3,7,8-tetrachlorodibenzo-p-dioxin	1989	Fundam Appl Toxicol. 1989 Nov;13(4):723-36. doi: 10.1016/0272-0590(89)90330-8.	Perfluorodecanoic acid (PFDA) is a 10-carbon straight-chain fatty acid. Its toxicity in rats has been reported to resemble that produced by exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Mice which are "responsive" to TCDD toxicity carry the Ahb allele, while mice homozygous for the Ahd gene are less sensitive to TCDD toxicity. To characterize the toxicity of PFDA and determine if it is under the control of the Ah locus, female responsive C57BL/6N (Ahb/b) mice and congenic C57BL/6J mice, differing only at the Ah locus (responsive, Ahb/b; heterozygous responsive, Ahb/d and "nonresponsive," Ahd/d), were administered a single oral dose of PFDA, at levels from 0 to 320 mg/kg body weight, observed daily for overt signs of toxicity, and weighed three times weekly. In the wild-type congenic C57BL/6J (Ahb/b) subline, mice were killed at 2, 7, 14, and 30 days following exposure. All other mice were killed on Day 30. Serum was taken from the C57BL/6N mice for analysis of thyroid hormone levels. Selected organs from all mice were weighed and fixed for histopathological examination. Dose-related mortality was observed as early as 5 days postexposure and time-to-death was inversely related to dose. Dramatic decreases in body weight occurred shortly following treatment in all strains. Serum triiodothyronine (T3) and thyroxine (T4) levels increased with increasing dose. There was a marked increase (p less than 0.05) in absolute and relative liver weights and a significant decrease in thymus weights. Hepatocellular hypertrophy was observed in all treated mice other than controls. A marked increase in hepatocyte peroxisomes was observed in all treatment groups. Thus, in contrast to TCDD, the acute toxicity of PFDA in the female C57BL/6 mouse does not vary with the Ah allele and is distinct from that reported for TCDD.			●	●						-		C	C
1253	実験動物（生殖発生毒性）	Henderson, W Matthew; Smith, Mary Alice	Perfluorooctanoic acid and perfluorononanoic acid in fetal and neonatal mice following in utero exposure to 8-2 fluorotelomer alcohol	2007	Toxicol Sci. 2007 Feb;95(2):452-61. doi: 10.1093/toxsci/kfl162. Epub 2006 Nov 8.	8-2 Fluorotelomer alcohol (FTOH) and its metabolites, perfluorooctanoic acid (PFOA) and perfluorononanoic acid (PFNA), are developmental toxicants but metabolism and distribution during pregnancy are not known. To examine this, timed-pregnant mice received a single gavage dose (30 mg 8-2 FTOH/kg body weight) on gestational day (GD) 8. Maternal and neonatal serum and liver as well as fetal and neonatal homogenate extracts were analyzed using gas chromatography coupled with mass spectrometry. During gestation (GD9 to GD18), maternal serum and liver concentrations of PFOA decreased from 789 +/- 41 to 668 +/- 23 ng/ml and from 673 +/- 23 to 587 +/- 55 ng/g, respectively. PFOA was transferred to the developing fetuses as early as 24-h posttreatment with concentrations increasing from 45 +/- 9 ng/g (GD10) to 140 +/- 32 ng/g (GD18), while PFNA was quantifiable only at GD18 (31 +/- 4 ng/g). Post-partum, maternal serum PFOA concentrations decreased from 451 +/- 21 ng/ml postnatal day (PND) 1 to 52 +/- 19 ng/ml (PND15) and PFNA concentrations, although fivefold less, exhibited a similar trend. Immediately after birth, pups were cross-fostered with dams that had been treated during gestation with 8-2 FTOH (T) or vehicle (C) resulting in four treatment groups in which the first letter represents in utero (fetal) exposure and the second represents lactational (neonatal) exposure: C/C, T/C, C/T, T/T. On PND1, neonatal whole-body homogenate concentrations of PFOA from T/T and T/C groups averaged 200 +/- 26 ng/g, decreased to 149 +/- 19 ng/g at PND3 and this decreasing trend was seen in both neonatal liver and serum from PND3 to PND15. Based on detectible amounts of PFOA in neonatal serum in the C/T group on PND3 (57 +/- 11 ng/ml) and on PND15 (58 +/- 3 ng/ml), we suggest that the neonates were exposed through lactation. In conclusion, exposure of neonates to PFOA and PFNA occurs both pre- and postnatally following maternal 8-2 FTOH exposure on GD8.			●	●						-		C	C
1254	実験動物（生殖発生毒性）	Hirata-Koizumi, Mutsuko; Fujii, Sakiko; Furukawa, Masatoshi; Ono, Atsushi; Hirose, Akihiko	Repeated dose and reproductive/developmental toxicity of perfluorooctadecanoic acid in rats	2012	J Toxicol Sci. 2012 Feb;37(1):63-79. doi: 10.2131/jts.37.63.	Male and female rats were given perfluorooctadecanoic acid (PFOdA) by gavage at 40, 200 or 1,000 mg/kg/day, and each female was mated with a male in the same dose group after 14-day administration. Males were dosed for 42 days and females were dosed throughout the gestation period until day 5 of lactation. One female given 1,000 mg/kg/day was euthanized on day 18 of gestation due to a moribund condition; however, no other treatment-related clinical signs of toxicity were observed. Body weights fell at 1,000 mg/kg/day from day 28 through the administration period in males and throughout gestation and lactation in females. Red blood cell count, hemoglobin level and hematocrit were decreased at 200 and 1,000 mg/kg/day in males and activated partial thromboplastin time was prolonged at 1,000 mg/kg/ day in females. Histopathological examination revealed hepatic changes, such as centrilobular hypertrophy and necrosis, in males given 200 and 1,000 mg/kg/day and in females given 1,000 mg/kg/day. Pancreatic zymogen granule was decreased in both sexes at 1,000 mg/kg/day. As for reproductive and developmental toxicity, there were decreases in the number of corpora lutea, implantation, total number of pups born and the number of live pups on postnatal days 0 and 4 at 1,000 mg/kg/day. At this dose, birth weights of pups were decreased and postnatal body weight gain was inhibited. Based on these findings, the NOAEL of PFOdA was considered to be 40 mg/kg/day for repeated dose toxicity and 200 mg/kg/day for reproductive/developmental toxicity.			●							-		C	C
1255	実験動物（生殖発生毒性）	Hirata-Koizumi M, Fujii S, Hina K, Matsumoto M, Takahashi M, Ono A and Hirose A	Repeated dose and reproductive/developmental toxicity of long-chain perfluoroalkyl carboxylic acids in rats: perfluorohexadecanoic acid and perfluorotetradecanoic acid	2015	Fundamental Toxicological Sciences, 2, 177–190. doi: 10.2131/fts.2.177	Perfluoroalkyl carboxylic acids (PFCAs) are global environmental contaminants that are the cause of concern due to their possible effects on wildlife and human health. Since few studies have investigated the toxicity of long-chain PFCAs, we have performed combined repeated dose toxicity studies with the reproduction/developmental toxicity screening tests. We previously examined perfluoroundecanoic acid (C11), perfluorododecanoic acid (C12), and perfluorooctadecanoic acid (C18). We herein reported our results for perfluorotetradecanoic acid (PFTeDA; C14) and perfluorohexadecanoic acid (PFHxDA: C16). Male and female rats were administered PFTeDA at 1, 3 or 10 mg/kg/day or PFHxDA at 4, 20 or 100 mg/kg/day by gavage, and each female was then mated with a male in the same dose group after 14 days. Males were dosed for a total of 42 days and females were dosed throughout the gestation period until day 5 after parturition. PFTeDA and PFHxDA caused hepatocyte hypertrophy and/or fatty changes in the liver at the middle and high doses. PFTeDA also induced follicular cell hypertrophy in the thyroid at the middle and high doses. The only reproductive/developmental effect observed was an inhibited postnatal body weight gain in pups in the 10 mg/kg/day PFTeDA group. Based on these results, the NOAELs for the repeated dose and reproductive/developmental toxicity were concluded to be 1 and 3 mg/kg/day for PFTeDA and 4 and 100 mg/kg/day for PFHxDA, respectively. Our current and previous results indicate that the toxicity of PFCAs decreases with increases in the carbon chain length from 12 to 18.			●							-		C	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献クラン①C	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1256	実験動物（生殖発生毒性）	Iwai, Hiroyuki; Hoberman, Alan M	Oral (Gavage) combined developmental and perinatal/postnatal reproduction toxicity study of ammonium salt of perfluorinated hexanoic acid in mice	2014	Int J Toxicol. 2014 May;33(3):219-237. doi: 10.1177/1091581814529449. Epub 2014 Apr 3.	The reproductive toxicity potential of Ammonium Salt of Perfluorinated Hexanoic Acid (PFHxA Ammonium Salt) in pregnant Crl: CD1(ICR) mice was investigated. Twenty females/group were administered the test substance or vehicle once daily from gestation day 6 through 18. Phase 1 doses: 0, 100, 350, and 500 mg/kg/d; phase 2: 0, 7, 35, and 175 mg/kg/d. Parameters evaluated include mortality, viability, body weights, clinical signs, abortions, premature deliveries, pregnancy and fertility, litter observations, maternal behavior, and sexual maturity in the F1 generation. The level of PFHxA Ammonium Salt was measured in the liver of F0 and F1 mice. At doses of 350 and 500 mg/kg/d maternal mortalities, excess salivation and changes in body weight gains occurred. Pup body weights were reduced on postpartum day (PPD) 0 in all the dosage groups, but persisted only in the 350 and 500 mg/kg/d groups. Additional effects at 300 and 500 mg/kg/d included stillbirths, reductions in viability indices, and delays in physical development. Levels of PFHxA Ammonium Salt in the livers of the 100 mg/kg/d dams were all below the lower limit of quantization (0.02 µg/mL); in the 350 mg/kg/d group, 3 of the 8 samples had quantifiable analytical results. In phase 2 no PFHxA Ammonium Salt was found in the liver. Adverse effects occurred only in the 175 mg/kg/d group and consisted of increased stillborn pups, pups dying on PPD 1, and reduced pup weights on PPD 1. Based on these data, the maternal and reproductive no observable adverse effect level of PFHxA Ammonium Salt is 100 mg/kg/d.			●	●						-		C	C
1257	実験動物（生殖発生毒性）	Iwai, Hiroyuki; Hoberman, Alan M; Goodrum, Philip E; Mendelsohn, Emma; Anderson, Janet K	Addendum to Iwai and Hoberman (2014)—reassessment of developmental toxicity of PFHxA in mice	2019	Int J Toxicol. 2019 May/Jun;38(3):183-191. doi: 10.1177/1091581819837904. Epub 2019 Apr 14.	This article presents a supplemental data analysis and evaluation of the findings from an oral (gavage) combined developmental and perinatal/postnatal reproduction toxicity study of the ammonium salt of perfluorohexanoic acid (CASRN: 21615-47-4) in Crl: CD-1(ICR) mice. The original study has been cited as supporting a lowest-observed-adverse-effects level of 175 mg/kg/d and no-observed-adverse-effects level of 35 mg/kg/d for developmental effects from perfluorohexanoic acid (PFHxA, CASRN: 307-24-4) in mice. The statistical analysis reported in 2014 was accurate in terms of quantifying statistical significance within phase 2 of the study. However, given the low incidence of findings, the purpose of this article is to extend the analysis and interpretation of findings by pooling the control group information from both phases of the same study, comparing the study findings to the incidence rates for stillbirths and postpartum viability for this species and strain of mouse observed for similar studies conducted by the same laboratory, and evaluating data on the incidence and range of spontaneous eye abnormalities reported in the literature. Based on this supplemental evaluation, the original study supports a NOAEL of 175 mg/kg/d for PFHxA in mice, which is a factor of 5-fold higher than previously reported. Furthermore, to the extent that this study may be considered in the selection of a point of departure for PFHxA in mice, it is noted that 175 mg/kg/d for maternal exposure is an unbounded NOAEL for developmental effects, meaning that the study did not establish a dose at which developmental effects may occur.			●							-		C	C
1258	実験動物（生殖発生毒性）	Kato, Hina; Fujii, Sakiko; Takahashi, Mika; Matsumoto, Mariko; Hirata-Koizumi, Mutsuko; Ono, Atsushi; Hirose, Akihiko	Repeated dose and reproductive/developmental toxicity of perfluorododecanoic acid in rats	2015	Environ Toxicol. 2015 Nov;30(11):1244-63. doi: 10.1002/tox.21996. Epub 2014 Apr 22.	Perfluoroalkyl carboxylic acids (PFCAs) are a series of environmental contaminants that have received attention because of their possible adverse effects on wildlife and human health. Although many toxicological studies have been performed on perfluorooctanoic acid with carbon chain length C8, available toxicity data on PFCAs with longer chains are still insufficient to evaluate their hazard. A combined repeated dose and reproductive/developmental toxicity screening study for perfluorododecanoic acid (PFDoA; C12) was conducted in accordance with OECD guideline 422 to fill these toxicity data gaps. PFDoA was administered by gavage to male and female rats at 0.1, 0.5, or 2.5 mg/kg/day. The administration of PFDoA at 0.5 and 2.5 mg/kg/day for 42-47 days mainly affected the liver, in which hypertrophy, necrosis, and inflammatory cholestasis were noted. Body weight gain was markedly inhibited in the 2.5 mg/kg/day group, and a decrease in hematopoiesis in the bone marrow and atrophic changes in the spleen, thymus, and adrenal gland were also observed. Regarding reproductive/developmental toxicity, various histopathological changes, including decreased spermatid and spermatozoa counts, were observed in the male reproductive organs, while continuous diestrous was observed in the females of the 2.5 mg/kg/day group. Seven of twelve females receiving 2.5 mg/kg/day died during late pregnancy while four other females in this group did not deliver live pups. No reproductive or developmental parameters changed at 0.1 or 0.5 mg/kg/day. Based on these results, the NOAELs of PFDoA were concluded to be 0.1 mg/kg/day for repeated dose toxicity and 0.5 mg/kg/day for reproductive/developmental toxicity.			●	●						-		C	C
1259	実験動物（生殖発生毒性）	Koskela, A; Finnilä, M A; Korkalainen, M; Spulber, S; Koponen, J; Håkansson, H; Tuukkanen, J; Viluksela, M	Effects of developmental exposure to perfluorooctanoic acid (PFOA) on long bone morphology and bone cell differentiation	2016	Toxicol Appl Pharmacol. 2016 Jun 15;301:14-21. doi: 10.1016/j.taap.2016.04.002. Epub 2016 Apr 9.	Perfluorooctanoic acid (PFOA) is a ubiquitous and persistent environmental chemical, which has been used extensively due to its stability and surface tension-lowering properties. Toxicological effects include induction of neonatal mortality and reproductive toxicity. In this study, pregnant C57BL/6 mice were exposed orally to 0.3mg PFOA/kg/day throughout pregnancy, and female offspring were studied at the age of 13 or 17months. Morphometrical and biomechanical properties of femurs and tibias were analyzed with micro-computed tomography and 3-point bending, and bone PFOA concentrations were determined by mass spectrometry. The effects of PFOA on bone cell differentiation were studied in osteoclasts from C57BL/6 mice and in the MC3T3 pre-osteoblast cell line. PFOA exposed mice showed increased femoral periosteal area as well as decreased mineral density of tibias. Biomechanical properties of these bones were not affected. Bone PFOA concentrations were clearly elevated even at the age of 17months. In osteoblasts, low concentrations of PFOA increased osteocalcin (OCN) expression and calcium secretion, but at PFOA concentrations of 100µM and above osteocalcin (OCN) expression and calcium secretion were decreased. The number of osteoclasts was increased at all PFOA concentrations tested and resorption activity dose-dependently increased from 0.1-1.0µM, but decreased at higher concentrations. The results show that PFOA accumulates in bone and is present in bones until the old age. PFOA has the potential to influence bone turnover over a long period of time. Therefore bone is a target tissue for PFOA, and altered bone geometry and mineral density seem to persist throughout the life of the animal.			●	●					●	-		C	B
1260	実験動物（生殖発生毒性）	Lee, Iwa; Viberg, Henrik	A single neonatal exposure to perfluorohexane sulfonate (PFHxS) affects the levels of important neuroproteins in the developing mouse brain	2013	Neurotoxicology. 2013 Jul;37:190-6. doi: 10.1016/j.neuro.2013.05.007. Epub 2013 May 20.	Perfluorohexane sulfonate (PFHxS) is an industrial chemical and belongs to the group of perfluorinated compounds (PFCs). It has recently been shown to cause developmental neurobehavioral defects in mammals. These compounds are commonly used in products such as surfactant and protective coating due to their ability to repel water- and oil stains. PFCs are globally found in the environment as well as in human umbilical cord blood, serum and breast milk. In a previous study on other well-known PFCs, i.e. PFOS and PFOA, it was shown that neonatal exposure caused altered neuroprotein levels in the hippocampus and cerebral cortex in neonatal male mice. The present study show that neonatal exposure to PFHxS, during the peak of the brain growth spurt, can alter neuroprotein levels, e.g. CaMKII, GAP-43, synaptophysin and tau, which are essential for normal brain development in mice. This was measured for both males and females, in hippocampus and cerebral cortex. The results suggest that PFHxS may act as a developmental neurotoxicant and the effects are similar to that of PFOS and PFOA, but also to other substances such as PCBs, PBDEs and bisphenol A.			●							-		C	C
1261	実験動物（生殖発生毒性）	Lieder, Paul H; York, Raymond G; Hakes, Daniel C; Chang, Shu-Ching; Butenhoff, John L	A two-generation oral gavage reproduction study with potassium perfluorobutanesulfonate (K+PFBS) in Sprague Dawley rats	2009	Toxicology. 2009 May 2;259(1-2):33-45. doi: 10.1016/j.tox.2009.01.027. Epub 2009 Feb 11.	Perfluorobutanesulfonate (PFBS) is a surfactant and degradation product of substances based on perfluorobutanesulfonyl fluoride. A two-generation reproductive rat study has been conducted with potassium PFBS (K(+)PFBS). Parental-generation (P) rats were dosed orally by gavage with 0, 30, 100, 300 and 1000mg K(+)PFBS/kg/day for 10 weeks prior to and through mating (males and females), as well as during gestation and lactation (females only). First generation (F1) pups were dosed similarly, beginning at weaning. Second generation (F2) pups were not directly dosed but potentially exposed to PFBS through placental transfer and nursing, and the study was terminated 3 weeks after their birth. Endpoints evaluated included body weight, food consumption, clinical signs, estrus cycling, sperm quality, pregnancy, natural delivery, litter outcomes, and developmental landmarks. The no-observable-adverse effect dose level (NOAEL) in the parental generations (P and F1) was 100mg/kg/day. In the 300 and 1000mg/kg/day dose group rats, there were (1) increased liver weight (absolute or relative) and corresponding increased incidence of adaptive hepatocellular hypertrophy (male only) and (2) increased incidence of minimal to mild microscopic findings in the medulla and papilla of the kidneys (male and female). There were no K(+)PFBS treatment-related effects on fertility or reproduction among the P or the F1 rats. There were no microscopic changes in male or female reproductive organs, and no biologically relevant effects on sperm parameters, mating, estrous cycles, pregnancy, and natural delivery in the P- or F1-generations. There were no K(+)PFBS treatment-related effects on survival of pups in the two-generation study. Litter size and average pup birth weight per litter were not statistically significantly different from controls in any dose group. In the F1-generation, terminal body weight was reduced in males at 1000mg/kg/day. Preputial separation was slightly delayed (approximately 2 days) at this dose, a finding consistent with the body weight reduction. Essentially no effects were observed in the F1 females. F2 pups had normal body weights. The reproductive NOAEL was >1000mg/kg/day in both generations.			●	●						-		B	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ラン①C	文献ラン②C
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1262	実験動物（生殖発生毒性）	Loveless, Scott E; Slezak, Brian; Serex, Tessa; Lewis, Joseph; Mukerji, Pushkor; O'Connor, John C; Donner, E Maria; Frame, Steven R; Korzeniowski, Stephen H; Buck, Robert C	Toxicological evaluation of sodium perfluorohexanoate	2009	Toxicology. 2009 Oct 1;264(1-2):32-44. doi: 10.1016/j.tox.2009.07.011. Epub 2009 Jul 24.	Sodium perfluorohexanoate [NaPFHx, F(CF(2))(5)CO(2)Na, CAS#2923-26-4] was evaluated in acute, 90-day subchronic, one-generation reproduction, developmental and in vitro genetic toxicity studies. In the subchronic/one-generation reproduction study, four groups of young adult male and female Crl:CD(SD) rats were administered NaPFHx daily for approximately 90 days by gavage at dosages of 0, 20, 100, or 500 mg/kg. Selected groups of rats were evaluated after 1- and 3-month recovery periods. Rats selected for reproductive evaluations were dosed for approximately 70 days prior to cohabitation, through gestation and lactation, for a total of about 4 months. The subchronic toxicity no observed adverse effect level (NOAEL) was 20mg/(kg day), based on nasal lesions observed at 100 and 500 mg/(kg day). No effects were observed for neurobehavioral endpoints. NaPFHx was a moderate inducer of hepatic peroxisomal beta-oxidation with a no observed effect level (NOEL) of 20 (male rats) and 100mg/(kg day) (female rats). Elevated hepatic beta-oxidation levels were observed following 1-month recovery in male and female rats at 500 mg/(kg day). No NaPFHx-related effects were observed on any reproductive parameters. The P(1) adult rat NOAEL was 20mg/(kg day), based on reduced body weight parameters, whereas the NOAEL for reproductive toxicity was 100 mg/(kg day), based on effects limited to reduced F(1) pup weights. In the developmental study, female rats were dosed via gavage on gestation day (GD) 6-20 with the same doses of NaPFHx administered in the subchronic study. The maternal and developmental toxicity NOAEL was 100 mg/(kg day), based on maternal and fetal body weight effects at 500 mg/(kg day). NaPFHx is therefore concluded not to present a reproductive or developmental hazard. NaPFHx genotoxicity studies showed no mutations in the bacterial reverse mutation (Ames) assay or chromosome aberrations in human lymphocytes treated with NaPFHx in vitro. The lowest NOAEL from all of the studies was 20mg/(kg day) in the subchronic study based on nasal lesions. Benchmark doses (BMDL10) for nasal lesions were 13 and 21 mg/(kg day) for male and female rats, respectively. The relevance of the nasal lesions to humans is not known.			●	●						-		C	C
1263	実験動物（生殖発生毒性）	Mylchreest, E; Munley, S M; Kennedy, G L Jr	Evaluation of the developmental toxicity of 8-2 telomer B alcohol	2005	Drug Chem Toxicol. 2005;28(3):315-28. doi: 10.1081/dct-200064491.	The potential maternal and developmental toxicity of 8-2 Telomer B Alcohol was assessed in rats. Groups of 22 time-mated female Crl:CD (SD)IGS BR rats were administered oral gavage doses as suspensions of 8-2 Telomer B Alcohol in aqueous 0.5% methylcellulose from day 6 through 20 of gestation (G) at daily doses of either 0, 50, 200, or 500 mg/kg. Under the conditions of this study, adverse maternal toxicity was produced at 500 mg kg(- 1) day(- 1) and consisted of maternal mortality, decreased body weights and body weight gains, and increased clinical observations of toxicity. One litter at 500 mg kg(- 1) day(- 1) consisted of one early resorption and was believed to be secondary to overt maternal toxicity, although single conceptus litters occur historically in this strain of rats. Developmental toxicity at 500 mg kg(- 1) day(- 1) consisted of increased fetal skeletal variations (delayed pelvic bone ossification and wavy ribs). At 200 and 500 mg kg(- 1) day(- 1), there were transient reductions in maternal feed consumption. In addition, there were slight increases in the incidence of delayed fetal skull bone ossification at 200 and 500 mg kg(- 1) day(- 1). The no-observed-adverse-effect level (NOAEL), defined as the highest dose at which adverse effects attributable to the test substance were not detected, for both maternal and developmental toxicity, is considered to be 200 mg kg(- 1) day(- 1). Thus, 8-2 Telomer B Alcohol is not considered to be a selective developmental toxicant in rats. The transient and quantitative nature of the observations in the 200 mg/kg group supports the conclusion that these findings were not adverse.				●						-		C	C
1264	実験動物（生殖発生毒性）	Ramhøj, Louise; Hass, Ulla; Boberg, Julie; Scholze, Martin; Christiansen, Sofie; Nielsen, Flemming; Axelstad, Marta	Perfluorohexane sulfonate (PFHxS) and a mixture of endocrine disrupters reduce thyroxine levels and cause antiandrogenic effects in rats	2018	Toxicol Sci. 2018 Jun 1;163(2):579-591. doi: 10.1093/toxsci/kfy055.	The developmental toxicity of perfluorohexane sulfonate (PFHxS) is largely unknown despite widespread environmental contamination and presence in human serum, tissues and milk. To thoroughly investigate PFHxS toxicity in developing rats and to mimic a realistic human exposure situation, we examined a low dose close to human relevant PFHxS exposure, and combined the dose-response studies of PFHxS with a fixed dose of 12 environmentally relevant endocrine disrupting chemicals (EDmix). Two reproductive toxicity studies in time-mated Wistar rats exposed throughout gestation and lactation were performed. Study 1 included control, two doses of PFHxS, and two doses of PFHxS + EDmix (n = 5-7). Study 2 included control, 0.05, 5, or 25 mg/kg body weight/day PFHxS, EDmix-only, 0.05, 5, or 25 mg PFHxS/kg plus EDmix (n = 13-20). PFHxS caused no overt toxicity in dams and offspring but decreased male pup birth weight and slightly increased liver weights at high doses and in combination with the EDmix. A marked effect on T4 levels was seen in both dams and offspring, with significant reductions from 5 mg/kg/day. The EDmix caused antiandrogenic effects in male offspring, manifested as slight decreases in anogenital distance, increased nipple retention and reductions of the weight of epididymides, ventral prostrate, and vesicular seminalis. PFHxS can induce developmental toxicity and in addition results of the co-exposure studies indicated that PFHxS and the EDmix potentiate the effect of each other on various endpoints, despite their different modes of action. Hence, risk assessment may underestimate toxicity when mixture toxicity and background exposures are not taken into account.			●	●						-		C	B
1265	実験動物（生殖発生毒性）	Shi, Zhimin; Zhang, Hongxia; Ding, Lina; Feng, Yixing; Xu, Muqi; Dai, Jiayin	The effect of perfluorododecanonic acid on endocrine status, sex hormones and expression of steroidogenic genes in pubertal female rats	2009	Reprod Toxicol. 2009 Jun;27(3-4):352-359. doi: 10.1016/j.reprotox.2009.02.008. Epub 2009 Feb 25.	Perfluorododecanoic acid (PFDoA), one of a number of commercially important perfluoroalkyl acids, has been detected in sera from humans and other animals; however, the effects of PFDoA on female reproduction remain unclear. To assess the impact of PFDoA on puberty and endocrine status, we exposed weaned pre-pubertal female rats to PFDoA, administered orally at doses of 0, 0.5, 1.5 and 3mg/kg-d for 28 days, and measured body weight, reproductive organ weight and morphology, pubertal indicators, endocrine hormones, total serum cholesterol levels and steroidogenic enzyme gene expression. At 3mg/kg-d, PFDoA significantly decreased body weight and serum estradiol levels, increased cholesterol levels (p<0.05), and altered ovarian expression of genes responsible for cholesterol transport and steroidogenesis, including steroidogenic acute regulatory protein, cholesterol side-chain cleavage enzyme and 17-beta-hydroxysteroid dehydrogenase (p<0.05). PFDoA at the highest dose also reduced estrogen receptor alpha and beta expression levels in the ovary (p<0.05), whereas a lower concentration of PFDoA (0.5mg/kg-d) decreased estrogen receptor beta mRNA levels in the uterus (p<0.05). PFDoA treatment did not affect serum follicle-stimulating hormone or luteinizing hormone (LH) levels at any concentration, although PFDoA at 3mg/kg-d reduced LH receptor mRNA levels. There were no marked changes in sexual organ weight, age and weight at vaginal opening or first estrous cycle, or ovarian/uterine histology at any PFDoA concentration. These data show that PFDoA does not affect the endocrine status of pubertal rats, but at higher doses it does impact estradiol production and the expression of some key genes responsible for estrogen synthesis.			●	●						-		C	C
1266	実験動物（生殖発生毒性）	Shi, Zhimin; Ding, Lina; Zhang, Hongxia; Feng, Yixing; Xu, Muqi; Dai, Jiayin	Chronic exposure to perfluorododecanoic acid disrupts testicular steroidogenesis and the expression of related genes in male rats	2009	Toxicol Lett. 2009 Aug 10;188(3):192-200. doi: 10.1016/j.toxlet.2009.04.014. Epub 2009 May 3.	Perfluorododecanoic acid (PFDoA), a synthetic perfluorinated chemical, has been detected in environmental matrices, wildlife, and human serum. Its potential health risk for humans and animals has raised public concern. However, the effects of chronic PFDoA exposure on male reproduction remain unknown. The aim of this study was to determine the effects of chronic PFDoA exposure (110 days) on testosterone biosynthesis and the expression of genes related to steroidogenesis in male rats. In this study, we examined the serum levels of sex hormones, growth hormone, and insulin in male rats. Testicular morphology and the expression of key genes and proteins in testosterone biosynthesis were also analyzed. Markedly decreased serum testosterone levels were recorded after 110 days of PFDoA exposure at 0.2mg PFDoA/kg/day and 0.5mg PFDoA/kg/day, and cast-off cells were observed in some seminiferous tubules in testes exposed to 0.5mg PFDoA/kg/day. PFDoA exposure resulted in significantly decreased protein levels of steroidogenic acute regulatory protein (StAR) and cholesterol side-chain cleavage enzyme (P450scc), along with significantly reduced mRNA levels of insulin-like growth factor I (IGF-I), insulin-like growth factor I receptor (IGF-IR), and interleukin 1alpha (IL-1alpha) in rat testes at 0.2mg/kg/day and 0.5mg/kg/day. In addition, PFDoA exposure also affected the expression of some genes in the hypothalamo-neurohypophyseal system. However, PFDoA did not affect the expression of 5alpha-reductase, 3alpha-hydroxysteroid dehydrogenase, or aromatase in testis and liver. These findings demonstrate that chronic PFDoA exposure disrupts testicular steroidogenesis and expression of related genes in male rats. Multiple factors may be involved in the inhibition of testosterone by PFDoA.			●	●						-		C	C
1267	実験動物（生殖発生毒性）	Singh, Shilpi; Singh, Shio Kumar	Effect of gestational exposure to perfluorononanoic acid on neonatal mice testes	2019	J Appl Toxicol. 2019 Dec;39(12):1663-1671. doi: 10.1002/jat.3883. Epub 2019 Aug 6.	Perfluoroalkyl acids (PFAAs) are widely used in commercial products and are found in many goods of daily use. Perfluorononanoic acid (PFNA) is one of the PFAAs that possesses endocrine disrupting properties and we have recently shown that PFNA affects testicular functions in Parkes mice. Exposure to environmental endocrine disruptors during fetal life is believed to affect gonadal development and they might produce reproductive abnormalities in males. Therefore, the present study examined the effect of gestational exposure to PFNA on the testes of neonatal mice offspring. Pregnant Parkes mice were orally administered PFNA (2 and 5 mg/kg body weight) or distilled water from gestational day 12 until parturition. Male pups were killed on postnatal day 3. PFNA treatment decreased testosterone biosynthesis by inhibiting expression of steroidogenic acute regulatory protein, cytochrome P450scc, and 3β- and 17β-hydroxysteroid dehydrogenase; proliferation of testicular cells was also affected in treated mice. Furthermore, a marked decrease in expression of Wilms tumor 1, steroidogenic factor 1 and insulin-like factor 3 was noted in neonatal mice testes, indicating that the PFNA treatment may affect the development of the testis. Moreover, observation of the dose-related expression of anti-müllerian hormone and c-Kit in neonatal mice testes is also suggestive of an interference with gonadal development by PFNA exposure. In conclusion, the results suggest that the gestational exposure to PFNA decreased testosterone biosynthesis and altered the expression of critical factors involved in the development of the testis, thereby advocating a potential risk of PFNA to male reproductive health.			●							-		C	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①C	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1268	実験動物（生殖発生毒性）	Singh, Shilpi; Singh, Shio Kumar	Chronic exposure to perfluorononanoic acid impairs spermatogenesis, steroidogenesis and fertility in male mice	2019	J Appl Toxicol. 2019 Mar;39(3):420-431. doi: 10.1002/jat.3733. Epub 2018 Oct 7.	Perfluoroalkyl acids (PFAAs) are widely used in commercial applications and that they are ubiquitous and persistent in the environment. Perfluorononanoic acid (PFNA), a member of PFAAs, has been detected in human and wildlife. Previous acute exposure studies have shown the adverse effect of PFNA on the testis. The present study was aimed to examine the effect of chronic PFNA exposure, from prepuberty to adulthood, on testicular functions and fertility in Parkes (P) male mice and to investigate the possible mechanism(s) of its action. PFNA (0.2 and 0.5 mg/kg) was orally administered to P male mice for 90 days from prepuberty (postnatal day [PND] 25) to adulthood (PND 114). Histologically, testes in PFNA-treated mice showed non-uniform degenerative changes in the seminiferous tubules. The treatment also had adverse effects on testicular expression of steroidogenic markers, serum levels of cholesterol and testosterone, sperm parameters and on litter size. A marked increase in the level of lipid peroxidation and decrease in the activities of antioxidant enzymes were observed in the testis of PFNA-treated mice compared to controls. Further, a significant decrease in expression of proliferating cell nuclear antigen (PCNA) and in the number of PCNA-positive cells, and an increase in expression of caspase-3 were also noted in PFNA-treated mice testis. In conclusion, the results suggest that chronic exposure to PFNA in male mice interferes with testosterone biosynthesis and causes oxidative stress in the testis, leading to alterations in spermatogenesis, sperm quality and fertility potential.			●	●						-		C	C
1269	実験動物（生殖発生毒性）	Singh, Shilpi; Singh, Shio Kumar	Acute exposure to perfluorononanoic acid in prepubertal mice: effect on germ cell dynamics and an insight into the possible mechanisms of its inhibitory action on testicular functions	2019	Ecotoxicol Environ Saf. 2019 Nov 15;183:109499. doi: 10.1016/j.ecoenv.2019.109499. Epub 2019 Aug 6.	Perfluoroalkyl acids (PFAAs) are anthropogenic compounds used globally in a variety of commercial products. Perfluorononanoic acid (PFNA), a member of PFAAs, is detected in human blood and this has been reported to cause hepatotoxic, immunotoxic, and developmental and testicular toxic effects in laboratory animals. We have recently shown that the acute exposure to PFNA in prepubertal Parkes (P) mice impairs spermatogenesis by inducing oxidative stress and inhibiting testosterone biosynthesis in the testis. The present study was aimed to examine the effect of acute exposure to PFNA in prepubertal P mice on germ cell dynamics and to understand the possible mechanisms of action of this compound on testicular functions. PFNA (2 and 5 mg/kg body weight) was orally administered to male mice for 14 days from postnatal day 25-38. The treatment caused a decrease in overall germ cell transformation. The results also reveal that impairment in testicular functions in treated mice is associated with alterations in cholesterol and glucose homeostasis; further, an inhibition in expressions of growth hormone receptor (GHR), insulin-like growth factor-1 (IGF-1), insulin-like growth factor-1 receptor (IGF-1R), androgen receptor (AR), phosphorylated mammalian target of rapamycin (p-mTOR) and peroxisome proliferator activated receptor α (PPAR α) in the testis is also implicated in this action. The findings thus suggest involvement of multiple factors which altogether contribute to the alterations in spermatogenic process and testosterone production following acute exposure to PFNA in prepubertal mice.			●							-		C	C
1270	実験動物（生殖発生毒性）	Singh, Shilpi; Singh, Shio Kumar	Prepubertal exposure to perfluorononanoic acid interferes with spermatogenesis and steroidogenesis in male mice	2019	Ecotoxicol Environ Saf. 2019 Apr 15;170:590-599. doi: 10.1016/j.ecoenv.2018.12.034. Epub 2018 Dec 18.	Perfluoroalkyl acids (PFAAs) are widely used in industrial and commercial products and possess endocrine disrupting properties. Perfluorononanoic acid (PFNA), one of PFAAs, has been mainly reported to produce testicular toxicity in adult animals. The objective of the present study was to examine the effect of acute exposure of PFNA to prepubertal male Parkes (P) mice on spermatogenesis and testicular steroidogenesis, and to study the possible mechanism(s) of its action. PFNA (2 and 5 mg/kg) was orally administered to male P mice for 14 days from postnatal day 25-38. Histologically, testis in PFNA-treated mice showed non-uniform diverse degenerative changes in the seminiferous tubules; both normal and affected tubules were seen in the same testicular sections. The treatment caused a reduction in intra-testicular and serum testosterone levels accompanied by a decrease in testicular expression of SF1, StAR, CYP11A1, and 3β- and17β-HSD. Further, the activity of antioxidant enzymes and expression of Nrf2 and HO-1 in the testis were markedly decreased, while the level of lipid peroxidation and expression of IKKβ, NF-κB and caspase-3 were significantly increased in testis of PFNA-treated mice. There was also a decrease in PCNA expression and in PCNA-index and an increase in TUNEL-positive germ cells in testes of PFNA-treated mice. In conclusion, the results suggest that PFNA exposure to prepubertal male mice altered antioxidant enzymes activity and Nrf2-HO-1 signaling, leading to oxidative stress and a decrease in testosterone biosynthesis in the testis; these changes, in turn, caused increased apoptosis and decreased proliferation of germ cells, thereby suppression of spermatogenesis.			●							-		C	C
1271	実験動物（生殖発生毒性）	Takahashi, Mika; Ishida, Shigeru; Hirata-Koizumi, Mutsuko; Ono, Atsushi; Hirose, Akihiko	Repeated dose and reproductive/ developmental toxicity of perfluoroundecanoic acid in rats	2014	J Toxicol Sci. 2014 Feb;39(1):97-108. doi: 10.2131/jts.39.97.	Perfluoroalkyl acids (PFAAs) are environmental contaminants that have received attention because of their possible effects on wildlife and human health. In order to obtain initial risk information on the toxicity of perfluoroundecanoic acid (PFUA), we conducted a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD test guideline 422). PFUA was administered by gavage to rats at 0 (vehicle: corn oil), 0.1, 0.3 or 1.0 mg/kg/day. At 1.0 mg/kg/day, body weight gain was inhibited in both sexes, and there was a decrease in fibrinogen in both sexes and shortening of the activated partial thromboplastin time in males. An increase in blood urea nitrogen and a decrease in total protein in both sexes and increases in alkaline phosphatase and alanine transaminase and a decrease in albumin in males were observed at 1.0 mg/kg/day. Liver weight was increased in males at 0.3 mg/kg/day and above and in females at 1.0 mg/kg/day, and this change was observed after a recovery period. In both sexes, centrilobular hypertrophy of hepatocytes was observed at 0.3 mg/kg/day and above and focal necrosis was observed at 1.0 mg/kg/day. In reproductive/developmental toxicity, body weight of pups at birth was lowered and body weight gain at 4 days after birth was inhibited at 1.0 mg/kg/day, while no dose-related changes were found in the other parameters. Based on these findings, the no observed adverse effect levels (NOAELs) for the repeated dose and reproductive/developmental toxicity were considered to be 0.1 mg/kg/day and 0.3 mg/kg/day, respectively.			●	●						-		C	C
1272	実験動物（生殖発生毒性）	Viberg, Henrik; Lee, Iwa; Eriksson, Per	Adult dose-dependent behavioral and cognitive disturbances after a single neonatal PFHxS dose	2013	Toxicology. 2013 Feb 8;304:185-91. doi: 10.1016/j.tox.2012.12.013. Epub 2012 Dec 31.	Perfluoroalkyl acids, including perfluorohexane sulfonate (PFHxS), are fluorinated organic compounds used as surfactants and water and stain repellents in carpets, paper, and textiles, with characteristics to bioaccumulate and biomagnify in the food chain. PFHxS is found in umbilical cord blood, human milk and child serum from all over the world. We have recently reported that neonatal exposure to certain perfluoroalkyl acids, PFOS and PFOA, can induce persistent aberrations in spontaneous behavior and also affect learning and memory functions in the adult animal. The present study indicates that a single exposure to PFHxS on postnatal day 10, during a vulnerable period of brain development can alter adult spontaneous behavior and cognitive function in both male and female mice, effects that are both dose-response related and long-lasting/irreversible. PFHxS affected the cholinergic system, manifested as altered nicotine-induced behavior in adult animals. This is also in agreement with earlier studies on neonatal exposure to PFOS and PFOA. The present findings show that PFHxS, a member of the perfluoroalkyl acid group, can act as a developmental neurotoxicant and affect the cholinergic system and cognitive function and the effects show similarities with effects earlier reported after neonatal exposure to other POPs, such as bisphenol A, PBDEs and PCBs.			●	●						-		C	C
1273	実験動物（生殖発生毒性）	White, Sally S; Calafat, Antonia M; Kuklenyik, Zsuzsanna; Villanueva, LaTonya; Zehr, Robert D; Helfant, Laurence; Strynar, Mark J; Lindstrom, Andrew B; Thibodeaux, Julie R; Wood, Carmen; Fenton, Suzanne E	Gestational PFOA exposure of mice is associated with altered mammary gland development in dams and female offspring	2007	Toxicol Sci. 2007 Mar;96(1):133-44. doi: 10.1093/toxsci/kfl177. Epub 2006 Nov 28.	Perfluorooctanoic acid (PFOA), with diverse and widespread commercial and industrial applications, has been detected in human and wildlife sera. Previous mouse studies linked prenatal PFOA exposure to decreased neonatal body weights (BWs) and survival in a dose-dependent manner. To determine whether effects were linked to gestational time of exposure or to subsequent lactational changes, timed-pregnant CD-1 mice were orally dosed with 5 mg PFOA/kg on gestation days (GD) 1-17, 8-17, 12-17, or vehicle on GD 1-17. PFOA exposure had no effect on maternal weight gain or number of live pups born. Mean pup BWs on postnatal day (PND) 1 in all PFOA-exposed groups were significantly reduced and decrements persisted until weaning. Mammary glands from lactating dams and female pups on PND 10 and 20 were scored based on differentiation or developmental stages. A significant reduction in mammary differentiation among dams exposed GD 1-17 or 8-17 was evident on PND 10. On PND 20, delays in normal epithelial involution and alterations in milk protein gene expression were observed. All exposed female pups displayed stunted mammary epithelial branching and growth at PND 10 and 20. While control litters at PND 10 and 20 had average scores of 3.1 and 3.3, respectively, all treated litters had scores of 1.7 or less, with no progression of duct epithelial growth evident over time. BW was an insignificant covariate for these effects. These findings suggest that in addition to gestational exposure, abnormal lactational development of dams may play a role in early growth retardation of developmentally exposed offspring.			●	●		●	●		●	-		C	C
1274	実験動物（生殖発生毒性）	Xia, Wei; Wan, Yanjian; Li, Yuan-yuan; Zeng, Huaicai; Lv, Ziquan; Li, Gengqi; Wei, Zhengzheng; Xu, Shun-qing	PFOS prenatal exposure induce mitochondrial injury and gene expression change in hearts of weaned SD rats	2011	Toxicology. 2011 Mar 28;282(1-2):23-9. doi: 10.1016/j.tox.2011.01.011. Epub 2011 Jan 18.	Xenobiotics exposure in early life may have adverse effects on animals' development through mitochondrial injury or dysfunction. The current study demonstrated the possibility of cardiac mitochondrial injury in prenatal PFOS-exposed weaned rat heart. Pregnant Sprague-Dawley (SD) rats were exposed to perfluorooctane sulfonate (PFOS) at doses of 0.1, 0.6 and 2.0 mg/kg/d and 0.05% Tween 80 as control by gavage from gestation days 2-21. The dams were allowed to give nature delivery and then heart tissues from weaned (postnatal day 21) offspring rats were analyzed for mitochondrial injury through ultrastructure observation by electron microscope, global gene expression profile by microarray, as well as related mRNA and proteins expression levels by quantitative PCR and western blot. Ultrastructural analysis revealed significant vacuolization and inner membrane injury occurred at the mitochondria of heart tissues from 2.0 mg/kg/d dosage group. Meanwhile, the global gene expression profile showed significant difference in level of some mRNA expression associated with mitochondrial function at 2.0 mg/kg/d dosage group, compared to the control. Furthermore, dose-response trends for the expression of selected genes were analyzed by quantitative PCR and western blot analysis. The selected genes were mainly focused on those encoding for proteins involved in energy production, control of ion levels, and maintenance of heart function. The down-regulation of mitochondrial ATP synthetase (ATP5E, ATP5I and ATP5O) implicated a decrease in energy supply. This was accompanied by down-regulation of gene transcripts involved in energy consumption such as ion transporting ATPase (ATP1A3 and ATP2B2) and inner membrane protein synthesis (SLC25A3, SLC25A4, SLC25A10, SLC25A29). The up-regulation of gene transcripts encoding for uncoupling proteins (UCP1 and UCP3), epidermal growth factor receptor (EGFR) and connective tissue growth factor (CTGF), was probably a protective process to maintain heart function. The results indicate PFOS prenatal exposure can induce cardiac mitochondrial injury and gene transcript change, which may be a significant mechanism of the developmental toxicity of PFOS to rat.			●	●					●	-		C	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1275	実験動物（生殖発生毒性）	Zhao, Yong; Tan, Ying S; Strynar, Mark J; Perez, Gloria; Haslam, Sandra Z; Yang, Chengfeng	Perfluorooctanoic acid effects on ovaries mediate its inhibition of peripubertal mammary gland development in Balb/c and C57Bl/6 mice	2012	Reprod Toxicol. 2012 Jul;33(4):563-576. doi: 10.1016/j.reprotox.2012.02.004. Epub 2012 Mar 5.	Exposure to perfluorooctanoic acid (PFOA), a synthetic perfluorinated compound and an agonist of peroxisome proliferator-activated receptor α (PPARα), causes stunted mouse mammary gland development in various developmental stages. However, the underlying mechanisms remain poorly understood. We found that peripubertal PFOA exposure significantly inhibited mammary gland growth in both Balb/c and C57Bl/6 wild type mice, but not in C57Bl/6 PPARα knockout mice, and Balb/c mice were more sensitive to PFOA inhibition. PFOA caused (1) delayed or absence of vaginal opening and lack of estrous cycling during the experimental period; (2) decreases in ovarian steroid hormonal synthetic enzyme levels; and (3) reduced expression of estrogen- or progesterone-induced mammary growth factors. Supplementation with exogenous estrogen and/or progesterone reversed the PFOA inhibitory effect on mammary gland. These results indicate that PFOA effects on ovaries mediate its inhibition of mammary gland development in Balb/c and C57Bl/6 mice and that PPARα expression is a contributing factor.			●			●			●	-		C	C
1276	実験動物（生殖発生毒性）	Zhao, Binghai; Li, Li; Liu, Jieting; Li, Hongzhi; Zhang, Chunlei; Han, Pengfei; Zhang, Yufei; Yuan, Xiaohuan; Ge, Ren Shan; Chu, Yanhui	Exposure to perfluorooctane sulfonate in utero reduces testosterone production in rat fetal Leydig cells	2014	PLoS One. 2014 Jan 14;9(1):e78888. doi: 10.1371/journal.pone.0078888. eCollection 2014.	BACKGROUND: Perfluorooctane sulfonate (PFOS) is a synthetic material that has been widely used in industrial applications for decades. Exposure to PFOS has been associated with decreased adult testosterone level, and Leydig cell impairment during the time of adulthood. However, little is known about PFOS effects in utero on fetal Leydig cells (FLC). METHODS AND RESULTS: The present study investigated effects of PFOS on FLC function. Pregnant Sprague Dawley female rats received vehicle (0.05% Tween20) or PFOS (5, 20 mg/kg) by oral gavage from gestational day (GD) 11-19. At GD20, testosterone (T) production, FLC numbers and ultrastructure, testicular gene and protein expression levels were examined. The results indicate that exposures to PFOS have affected FLC function as evidenced by decreased T production, impaired FLC, reduced FLC number, and decreased steroidogenic capacity and cholesterol level in utero. CONCLUSION: The present study shows that PFOS is an endocrine disruptor of male reproductive system as it causes reduction of T production and impairment of rat fetal Leydig cells.			●						●	-		C	C
1277	実験動物（生殖発生毒性）	Abbott BD.	Review of the expression of peroxisome proliferator-activated receptors alpha (PPARα), beta (PPARβa), and gamma (PPARγ) in rodent and human development	2009	Reprod Toxicol. 2009 Jun;27(3-4):246-257. doi: 10.1016/j.reprotox.2008.10.001. Epub 2008 Oct 18.	The peroxisome proliferator-activated receptors (PPAR) belong to the nuclear hormone receptor superfamily and there are three primary subtypes, PPARalpha, beta, and gamma. These receptors regulate important physiological processes that impact lipid homeostasis, inflammation, adipogenesis, reproduction, wound healing, and carcinogenesis. These nuclear receptors have important roles in reproduction and development and their expression may influence the responses of an embryo exposed to PPAR agonists. PPARs are relevant to the study of the biological effects of the perfluorinated alkyl acids as these compounds, including perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), activate PPARalpha. Exposure of the rodent to PFOA or PFOS during gestation results in neonatal deaths, developmental delay and growth deficits. Studies in PPARalpha knockout mice demonstrate that the developmental effects of PFOA, but not PFOS, depend on expression of PPARalpha. This review provides an overview of PPARalpha, beta, and gamma protein and mRNA expression during mouse, rat, and human development. The review presents the results from many published studies and the information is organized by organ system and collated to show patterns of expression at comparable developmental stages for human, mouse, and rat. The features of the PPAR nuclear receptor family are introduced and what is known or inferred about their roles in development is discussed relative to insights from genetically modified mice and studies in the adult.				●						-		C	C
1278	実験動物（生殖発生毒性）	Feng, Yixing; Fang, Xuemei; Shi, Zhimin; Xu, Muqi; Dai, Jiayin	Effects of PFNA exposure on expression of junction-associated molecules and secretory function in rat Sertoli cells	2010	Reprod Toxicol. 2010 Nov;30(3):429-37. doi: 10.1016/j.reprotox.2010.05.010. Epub 2010 May 16.	Perfluorononanoic acid (PFNA, C9), a synthetic perfluorinated chemical containing nine carbons, has been identified in humans and wildlife worldwide. Sertoli cell plays a key role in spermatogenesis; however, the toxic effects of PFNA on Sertoli cells have not been studied. The aim of this study was to investigate the effects of PFNA exposure on cell junction molecules and factors specifically secreted by Sertoli cells. Primary Sertoli cells from 20- to 21-day-old rats were exposed to increasing PFNA concentrations (0, 1, 10, 25, 50, or 75 μM) for 24h. No significant changes in the expression of cytoskeleton-associated molecules were noted, although the mRNA levels of vimentin were upregulated dramatically in cells exposed to 50 and 75 μM PFNA. Meanwhile, the mRNA levels of Sertoli cell-specific secretions, such as Mullerian inhibiting substance (MIS), androgen binding protein (ABP), inhibin B, transferrin, and follicle-stimulating hormone receptor (FSH-R) changed significantly in experimental groups. Wilms' tumor gene (WT1), a transcription factor, was upregulated significantly in cells exposed to 1-75 μM PFNA. In additional studies, male rats were exposed to 0, 1, 3, or 5mg/kg-d PFNA for 14 days. Vacuoles in the cytoplasm of Sertoli cells were observed in the ultrastructure of testis. Furthermore, the changes in the concentrations of MIS and inhibin B in serum and the protein levels of WT1 and transferrin in testis were similar to the mRNA expression levels of those observed after in vitro treatment. In conclusion, these findings demonstrated that PFNA treatment led to the damage of specific secretory functions of Sertoli cells and that these effects might be an underlying cause of the male-specific reproductive toxicity of PFNA.				●						-		C	C
1279	実験動物（生殖発生毒性）	Fuentes, Silvia; Colomina, M Teresa; Rodriguez, Judit; Vicens, Paloma; Domingo, José L	Interactions in developmental toxicology: Concurrent exposure to perfluorooctane sulfonate (PFOS) and stress in pregnant mice	2006	Toxicol Lett. 2006 Jun 20;164(1):81-9. doi: 10.1016/j.toxlet.2005.11.013. Epub 2005 Dec 27.	The maternal and developmental toxicity of combined exposure to restraint stress and perfluorooctane sulfonate (PFOS) was assessed in mice. On gestation Days 6-18, four groups of plug-positive female mice were orally exposed to PFOS at 0, 1.5, 3 and 6 mg/kg/day. Four additional groups of plug-positive animals received the same PFOS doses being restrained during 30 min three times per day. A control group was also included. Cesarean sections were performed on Day 18 of gestation and fetuses were weighed and examined for external, internal and skeletal malformations and variations. Before sacrifice of the dams, blood was collected and serum samples were prepared for thyroid hormones (total and free T3 and T4) and corticosterone analyses. The results of the present study show that both PFOS and restraint stress induced maternal toxicity. In turn, PFOS-induced fetal toxicity was evidenced by increased prenatal mortality. The only effect of restraint on fetal toxicity was a reduction on body weight and an increased prenatal mortality in fetuses concurrently exposed to 1.5 mg/kg of PFOS and restraint. PFOS-induced adverse effects on maternal and fetal toxicity in mice were observed at lower doses than those previously reported.				●						-		C	C
1280	実験動物（生殖発生毒性）	Fuentes, Silvia; Colomina, M Teresa; Vicens, Paloma; Domingo, José L	Influence of maternal restraint stress on the long-lasting effects induced by prenatal exposure to perfluorooctane sulfonate (PFOS) in mice	2007	Toxicol Lett. 2007 Jul 10;171(3):162-70. doi: 10.1016/j.toxlet.2007.05.006. Epub 2007 May 21.	The behavioral effects of concurrent maternal exposure to restraint stress and perfluorooctane sulfonate (PFOS) were assessed in the offspring of mice at 3 months of age. Plug positive females were divided into two groups. Animals were given by gavage 0 and 6mg PFOS/kg/day on gestation days 12-18. One-half of the animals in each group were subjected to restraint stress (30min/session, three sessions per day) during the same period. At 3 months, mice were evaluated for general activity in an open-field, and for learning and memory in a water maze task. The group prenatally exposed to PFOS and restraint presented a reduced mobility in the open-field. In the water maze, an interaction between sex and restraint was observed. Delayed task learning was also detected in females prenatally exposed to PFOS and restraint. An overall effect of restraint was observed in mice on retention of the task, suggesting a better retention in restrained animals. On the other hand, corticosterone levels were lower in animals prenatally subjected to restraint stress. The current results suggest interactive effects between PFOS and maternal stress.				●	●					-		C	C
1281	実験動物（生殖発生毒性）	Gortner EG, Lamprecht EG, Case MT.	Oral teratology study of T-3141CoC in rabbits	1982	St. Paul, MN: Riker Laboratories, Inc.	No abstract available				●						企業データ		D	D
1282	実験動物（生殖発生毒性）	Hallgren, Stefan; Fredriksson, Anders; Viberg, Henrik	More signs of neurotoxicity of surfactants and flame retardants - neonatal PFOS and PBDE 99 cause transcriptional alterations in cholinergic genes in the mouse CNS	2015	Environ Toxicol Pharmacol. 2015 Sep;40(2):409-16. doi: 10.1016/j.etap.2015.06.014. Epub 2015 Jul 18.	Maternally and lactionally transferred persistent organic pollutants may interfere with CNS development. Here, 10-day-old male mice were exposed to single oral doses of PFOS (perflouroctanosulphonate) or PBDE 99 (2,2',4,4',5-penta-bromodiphenyl ether), and examined for changes in cholinergic gene transcription in the CNS 24h and 7 weeks later. 24h after exposure qPCR analyses revealed decreased transcription of nAChR-β2 and AChE in cortex, and increased mAChR-5 in hippocampus of PFOS treated mice. Neonatal PFOS treatment altered spontaneous behaviour at 2 months of age but did not affect gene transcription in adults. At 2 months of age neonatally PBDE 99 treated mice had altered spontaneous behaviour, and cortical transcription of AChE, nAChR-α4, nAChR-β2 and mAChR-5 were elevated. Our results indicate that PFOS and PBDE 99 affects the developing central cholinergic system by altering gene transcription in cortex and hippocampus, which may in part account for mechanisms causing changes in spontaneous behaviour.				●						-		C	C
1283	実験動物（生殖発生毒性）	Hoberman AM, York RG.	Oral (gavage) combined repeated dose toxicity study of T-7706 with the reproduction/developmental toxicity screening test	2003	Argus Research. (Unpublished report)	No abstract available				●			●			企業データ		D	D
1284	実験動物（生殖発生毒性）	Jiang, Qixiao; Lust, Robert M; DeWitt, Jamie C	Perfluorooctanoic acid induced-developmental cardiotoxicity: Are peroxisome proliferator activated receptor α (PPARα) and bone morphorgenic protein 2 (BMP2) pathways involved? J Toxicol Environ Health A 76(11):635-650	2013	J Toxicol Environ Health A. 2013;76(11):635-50. doi: 10.1080/15287394.2013.789415.	Perfluorooctanoic acid (PFOA) is an environmental contaminant known to induce developmental toxicity in animal models through activation of the peroxisome proliferator-activated receptor α (PPARα). Previously, it was demonstrated that in ovo exposure to PFOA induced cardiotoxicity in chicken embryos and hatchlings. To investigate potential PPARα-mediated mechanisms, fertile chicken eggs were injected prior to incubation with WY 14,643, a PPARα agonist. Cardiac morphology and function were evaluated in late-stage embryos and hatchlings. Histologically, unlike PFOA, WY 14,643 did not induce thinning of the right ventricular wall. Via echocardiography, however, WY 14,643 induced effects similar to those of PFOA, including increased left ventricular wall thickness and mass, elevated heart rate, ejection fraction, fractional shortening, and decreased stroke volume. Additionally, to investigate mechanisms associated with early heart development, a separate group of fertile chicken eggs was injected prior to incubation with PFOA or WY 14,643 and in early-stage embryos, gene expression and protein concentration associated with the bone morphogenic protein (BMP2) pathway were determined. Although changes were not statistically consistent among doses, expression of BMP2, Nkx2.5, and GATA4 mRNA in early embryos was altered by PFOA exposure; however, protein concentrations of these targets were not markedly altered by either PFOA or WY 14,643. Protein levels of pSMAD1/5, a transcriptional regulator stimulated by BMPs, were altered by both PFOA and WY 14,643, but in different directions; PFOA reduced cytoplasmic pSMAD1/5, whereas WY 14,643 decreased nuclear pSMAD1/5. Taken together, these data suggest that developmental cardiotoxicity induced by PFOA likely involves both PPARα and BMP2 pathways.				●						-		D	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①D	文献クラン②C
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1285	実験動物（生殖発生毒性）	Jiang, Qixiao; Lust, Robert M; Strynar, Mark J; Dagnino, Sonia; DeWitt, Jamie C	Perfl[o]urooctanoic acid induces developmental cardiotoxicity in chicken embryos and hatchlings	2012	Toxicology. 2012 Mar 11;293(1-3):97-106. doi: 10.1016/j.tox.2012.01.005. Epub 2012 Jan 18.	Perfluorooctanoic acid (PFOA) is a widespread environmental contaminant that is detectable in serum of the general U.S. population. PFOA is a known developmental toxicant that induces mortality in mammalian embryos and is thought to induce toxicity via interaction with the peroxisome proliferator activated receptor alpha (PPARα). As the cardiovascular system is crucial for embryonic survival, PFOA-induced effects on the heart may partially explain embryonic mortality. To assess impacts of PFOA exposure on the developing heart in an avian model, we used histopathology and immunohistochemical staining for myosin to assess morphological alterations in 19-day-old chicken embryo hearts after PFOA exposure. Additionally, echocardiography and cardiac myofibril ATPase activity assays were used to assess functional alterations in 1-day-old hatchling chickens following developmental PFOA exposure. Overall thinning and thinning of a dense layer of myosin in the right ventricular wall were observed in PFOA-exposed chicken embryo hearts. Alteration of multiple cardiac structural and functional parameters, including left ventricular wall thickness, left ventricular volume, heart rate, stroke volume, and ejection fraction were detected with echocardiography in the exposed hatchling chickens. Assessment of ATPase activity indicated that the ratio of cardiac myofibril calcium-independent ATPase activity to calcium-dependent ATPase activity was not affected, which suggests that developmental PFOA exposure may not affect cardiac energetics. In summary, structural and functional characteristics of the heart appear to be developmental targets of PFOA, possibly at the level of cardiomyocytes. Additional studies will investigate mechanisms of PFOA-induced developmental cardiotoxicity.				●						-		D	C
1286	実験動物（生殖発生毒性）	Jiang, Qixiao; Ma, Weiping; Wu, Jie; Wingard, Christopher J; DeWitt, Jamie C	Perfluorooctanoic acid-induced toxicity in primary cultures of chicken embryo cardiomyocytes	2016	Environ Toxicol. 2016 Nov;31(11):1580-1590. doi: 10.1002/tox.22162. Epub 2015 Jun 22.	Perfluorooctanoic acid (PFOA) is a widespread environmental contaminant that induces developmental cardiotoxicity. It is detectable in late stage chicken embryos and hatchling chickens. To investigate mechanism(s) of cardiotoxicity, primary cultures of cardiomyocytes were prepared from 10-day-old chicken embryos that were (A) pre-exposed to vehicle or 2 mg of PFOA/kg of egg weight in ovo or (B) incubated with PFOA in vitro at concentrations ranging from 0 to 100 μg/mL in medium for 1 or 36 h. When viability was assessed, survival of cardiomyocytes prepared from pre-exposed embryos did not differ from vehicle controls, even under conditions of serum starvation designed to challenge the cells. However, 1 h of exposure to 100 μg/mL of PFOA in vitro and 36 h of exposure to 75 and 100 μg/mL PFOA in vitro decreased viability. When contractility was evaluated, cardiomyocytes cultured from pre-exposed embryos exhibited decreases in time to maximum departure velocity and cell length at peak contraction, whereas cardiomyocytes exposed in vitro exhibited a reduction in the 50% relaxation time at a concentration of 1 μg/mL relative to vehicle controls. Morphological assessment revealed decreased cardiomyocytes axial length following in ovo PFOA exposure and 24 h in vitro PFOA 50 μg/mL exposure. Reactive oxygen species (ROS) generation, which was evaluated only in cardiomyocytes exposed to PFOA in vitro, was significantly elevated following incubation with 50 μg/mL of PFOA for 1 h. These data indicate that while in vitro exposure to relatively high concentrations of PFOA can induce cytotoxicity and ROS, developmental cardiotoxicity observed in ovo is not likely mediated via PFOA-induced overt cytotoxicity, but likely by altering early cardiac morphologic and function processes. © 2015 Wiley Periodicals, Inc. Environ Toxicol 31: 1580-1590, 2016.				●						-		D	C
1287	実験動物（生殖発生毒性）	Koustas, Erica; Lam, Juleen; Sutton, Patrice; Johnson, Paula I; Atchley, Dylan S; Sen, Saunak; Robinson, Karen A; Axelrad, Daniel A; Woodruff, Tracey J	The Navigation Guide - evidence-based medicine meets environmental health: Systematic review of nonhuman evidence for PFOA effects on fetal growth	2014	Environ Health Perspect. 2014 Oct;122(10):1015-27. doi: 10.1289/ehp.1307177. Epub 2014 Jun 25.	BACKGROUND: In contrast to current methods of expert-based narrative review, the Navigation Guide is a systematic and transparent method for synthesizing environmental health research from multiple evidence streams. The Navigation Guide was developed to effectively and efficiently translate the available scientific evidence into timely prevention-oriented action. OBJECTIVES: We applied the Navigation Guide systematic review method to answer the question "Does fetal developmental exposure to perfluorooctanoic acid (PFOA) or its salts affect fetal growth in animals ?" and to rate the strength of the experimental animal evidence. METHODS: We conducted a comprehensive search of the literature, applied prespecified criteria to the search results to identify relevant studies, extracted data from studies, obtained additional information from study authors, conducted meta-analyses, and rated the overall quality and strength of the evidence. RESULTS: Twenty-one studies met the inclusion criteria. From the meta-analysis of eight mouse gavage data sets, we estimated that exposure of pregnant mice to increasing concentrations of PFOA was associated with a change in mean pup birth weight of -0.023 g (95% CI: -0.029, -0.016) per 1-unit increase in dose (milligrams per kilogram body weight per day). The evidence, consisting of 15 mammalian and 6 nonmammalian studies, was rated as "moderate" and "low" quality, respectively. CONCLUSION: Based on this first application of the Navigation Guide methodology, we found sufficient evidence that fetal developmental exposure to PFOA reduces fetal growth in animals.				●						-		C	C
1288	実験動物（生殖発生毒性）	Lee, Y Y; Wong, C K C; Oger, C; Durand, T; Galano, J-M; Lee, J C-Y	Prenatal exposure to the contaminant perfluorooctane sulfonate elevates lipid peroxidation during mouse fetal development but not in the pregnant dam	2015	Free Radic Res. 2015;49(8):1015-25. doi: 10.3109/10715762.2015.1027199. Epub 2015 Apr 24.	Perfluorooctane sulfonate (PFOS), a member of the perfluorinated chemical family, has been convincingly demonstrated to affect lipid metabolism in animals and humans and readily crosses the placenta to exert its effects on the developing fetuses. While its exact mechanism is still not clear, PFOS exposure has long been suggested to exert its toxicity via oxidative stress and/or altered gene expression. Levels of PFOS and malondialdehyde in various organs and cell cultures have been widely determined as general indicators of non-specific lipid peroxidation after PFOS exposure. In this study, the oxidation of precise polyunsaturated fatty acids and their metabolites, derived from enzymatic and non-enzymatic pathways was determined following PFOS exposure in both adult and maternal/fetal mice. CD-1 mice were exposed to 3 mg/kg body weight/day of PFOS in corn oil by oral gavage until late gestation (GD17). We demonstrated that lipid peroxidation was particularly and exclusively affected in fetuses exposed to PFOS, but this was not the case in the maternal mice, where limited effects were observed in the enzymatic oxidation pathway. In this study, we demonstrated that PFOS-induced lipid peroxidation might have a greater impact in free radical generation in fetuses than in dams and could be responsible for affecting fetal development. In addition, antioxidant enzymes, such as superoxide dismutase and catalase, appeared to maintain oxidative stress homeostasis partially in adult mice exposed to PFOS. Taken together, our results might elucidate the mechanism of how PFOS induces oxidative stress in vivo.				●						-		C	C
1289	実験動物（生殖発生毒性）	Li, Lili; Li, Xiaoheng; Chen, Xianwu; Chen, Yong; Liu, Jianpeng; Chen, Fenfen; Ge, Fei; Ye, Leping; Lian, Qingquan; Ge, Ren-Shan	Perfluorooctane sulfonate impairs rat Leydig cell development during puberty	2018	Chemosphere. 2018 Jan;190:43-53. doi: 10.1016/j.chemosphere.2017.09.116. Epub 2017 Sep 26.	Perfluorooctane sulfonate (PFOS) possibly delays male sexual development. However, its effects on pubertal Leydig cell development are unclear. The objective of the present study was to investigate the effects of in vivo PFOS exposure on rat Leydig cell development during puberty. Immature male Sprague Dawley rats were gavaged 5 or 10 mg/kg PFOS on postnatal day 35 for 21 days. Compared to the control (0 mg/kg), PFOS lowered serum testosterone levels without altering luteinizing hormone and follicle-stimulating hormone levels on postnatal day 56. PFOS in vivo downregulated mRNA or protein levels of Leydig cells (Lhcgr, Cyp11a1, and Cyp17a1). PFOS in vitro inhibited androgen secretion in immature Leydig cells at ≥ 50 nM, most possibly via downregulating Hsd17b3 mRNA level. At ≥ 500 nM, PFOS downregulated Lhcgr, inhibited BCL-2 and increased BAX levels to cause Leydig cell apoptosis. In conclusion, PFOS at a lower dose directly inhibited pubertal development of Leydig cells.				●						-		C	C
1290	実験動物（生殖発生毒性）	Liu, Wei; Li, Xiao; Xu, Lei; Liu, Li; Jin, Yihe; Sato, Itaru; Tsuda, Shuji	Influence of gestation, regular bleeding and intermittent exposure on blood perfluorooctane sulfonate levels in mice: Potential factors inducing sex difference and affecting exposure evaluation	2010	J Toxicol Sci. 2010 Jun;35(3):309-16. doi: 10.2131/jts.35.309.	Higher blood levels of perfluorooctane sulfonate (PFOS) in males than the females have been observed in many human biomonitoring studies, which is not well explained yet. The effects of gestation and regular bleeding on blood PFOS level in mice were investigated to evaluate the potential factors that could result in the sex difference. The mice were exposed to PFOS via drinking water at a concentration of 50 mug/l. After 6 weeks of pre-exposure and the gestation period, the blood PFOS concentrations in the gestagenic mice were significantly lower than the control non-gestagenic mice with a ratio of 0.45. Significant lower blood PFOS concentrations in the male mice treated by regular artificial bleeding were observed compared with those from the control male. However, such difference was not observed for the females. The sex difference in the effect of regular artificial bleeding on the blood PFOS level may be caused by the different accumulation and elimination rate in the female and male mice. In addition, the effect of intermittent exposure to PFOS on blood level was evaluated. Each single exposure caused a significant increase in blood PFOS level in both females and males, suggesting the acute exposure to PFOS occurred before the blood sampling, e.g. exposure to PFOS-contaminated foods or drinks, would affect the biomonitoring data to some extent depending on the background blood level. Thus serial blood monitoring is required to obtain accurate body burden.				●						-		C	C
1291	実験動物（生殖発生毒性）	Rosen, Mitchell B; Schmid, Judith E; Das, Kaberi P; Wood, Carmen R; Zehr, Robert D; Lau, Christopher	Gene expression profiling in the liver and lung of perfluorooctane sulfonate-exposed mouse fetuses: Comparison to changes induced by exposure to perfluorooctanoic acid	2009	Reprod Toxicol. 2009 Jun;27(3-4):278-288. doi: 10.1016/j.reprotox.2009.01.007. Epub 2009 Feb 6.	Perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) are environmental contaminants found in the tissues of humans and wildlife. They are activators of peroxisome proliferator-activated receptor-alpha (PPAR alpha) and exhibit hepatocarcinogenic potential in rats. PFOS and PFOA are also developmental toxicants in rodents and PFOS has been shown to induce pulmonary deficits in rat offspring. Pregnant CD-1 mice were dosed with 0, 5, or 10mg/kg PFOS from gestation days 1-17. Transcript profiling was conducted on the fetal liver and lung. Results were contrasted to data derived from a previous PFOA study. PFOS-dependent changes were primarily related to activation of PPAR alpha. No remarkable differences were found between PFOS and PFOA. Given that PPAR alpha signaling is required for neonatal mortality in PFOA-treated mice but not those exposed to PFOS, the neonatal mortality observed for PFOS may reflect functional deficits related to the physical properties of the chemical rather than to transcript alterations.				●						-		C	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ラン①C	文献ラン②C
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1292	実験動物（生殖発生毒性）	Rosen, Mitchell B; Thibodeaux, Julie R; Wood, Carmen R; Zehr, Robert D; Schmid, Judith E; Lau, Christopher	Gene expression profiling in the lung and liver of PFOA-exposed mouse fetuses	2007	Toxicology. 2007 Sep 24;239(1-2):15-33. doi: 10.1016/j.tox.2007.06.095. Epub 2007 Jun 29.	Perfluorooctanoic acid (PFOA) is a stable perfluoroalkyl acid used to synthesize fluoropolymers during the manufacture of a wide variety of products. Concerns have been raised over the potential health effects of PFOA because it is persistent in the environment and can be detected in blood and other tissues of many animal species, including humans. PFOA has also been shown to induce growth deficits and mortality in murine neonates. To better understand the mechanism of PFOA induced developmental toxicity, lung and liver gene expression profiling was conducted in PFOA-exposed full-term mouse fetuses. Thirty timed-pregnant CD-1 mice were orally dosed from gestation days 1-17 with either 0, 1, 3, 5, or 10mg/(kgday) PFOA in water. At term, fetal lung and liver were collected, total RNA prepared, and samples pooled from three fetuses per litter. Five biological replicates consisting of individual litter samples were then evaluated for each treatment group using Affymetrix mouse 430_2 microarrays. The expression of genes related to fatty acid catabolism was altered in both the fetal liver and lung. In the fetal liver, the effects of PFOA were robust and also included genes associated with lipid transport, ketogenesis, glucose metabolism, lipoprotein metabolism, cholesterol biosynthesis, steroid metabolism, bile acid biosynthesis, phospholipid metabolism, retinol metabolism, proteosome activation, and inflammation. These changes are consistent with transactivation of PPARalpha, although, with regard to bile acid biosynthesis and glucose metabolism, non-PPARalpha related effects were suggested as well. Additional studies will be needed to more thoroughly address the role of PPARalpha, and other nuclear receptors, in PFOA mediated developmental toxicity.				●						-		C	C
1293	実験動物（生殖発生毒性）	Shi, Zhimin; Zhang, Hongxia; Liu, Yang; Xu, Muqi; Dai, Jiayin	Alterations in gene expression and testosterone synthesis in the testes of male rats exposed to perfluorododecanoic acid	2007	Toxicol Sci. 2007 Jul;98(1):206-15. doi: 10.1093/toxsci/kfm070. Epub 2007 Mar 30.	Perfluorododecanoic acid (PFDoA, C12), a synthetic perfluorinated chemical containing 12 carbons, has broad industrial applications and has been detected in sera from humans and other animals; however, few reports have addressed the effects of PFDoA exposure on male reproduction. In the present study, the effects of PFDoA exposure on testes ultrastructure, testosterone levels, and steroidogenic gene expression were investigated. Male rats were orally dosed for 14 days with 1, 5, or 10 mg PFDoA/kg/day or with vehicle. Absolute testis weight was diminished at the highest dose while relative testes weight was markedly increased at doses of 5 and 10 mg/kg/day. Total serum cholesterol levels were significantly increased at the highest dose. While luteinizing hormone was significantly decreased at the highest dose, testosterone was markedly decreased at doses of 5 and 10 mg PFDoA/kg/day. Serum levels of follicle-stimulating hormone were not significantly affected by PFDoA, and estradiol levels were markedly decreased only at 5 mg/kg/day. Leydig cells, Sertoli cells, and spermatogenic cells from rats that received 5 or 10 mg PFDoA/kg/day, exhibited apoptotic features including dense irregular nuclei, condensed chromatin, ill-defined nuclear membranes, and abnormal mitochondria. PFDoA exposure resulted in significant declines in mRNA expression of several genes involved in cholesterol transport and steroid biosynthesis at doses of 5 and 10 mg PFDoA/kg/day, while the gene expression of luteinizing hormone receptor and aromatase was not significantly changed. Our results demonstrate that PFDoA affects the reproduction function of male rats via alterations in steroidogenesis genes, testosterone levels, and testes ultrastructure.				●						-		C	C
1294	実験動物（生殖発生毒性）	Wan, Hin-Ting; Mruk, Dolores D; Wong, Chris K C; Cheng, C Yan	Perfluorooctanesulfonate (PFOS) perturbs male rat Sertoli cell blood-testis barrier function by affecting F-actin organization via p-FAK-Tyr(407): An in vitro study	2014	Endocrinology. 2014 Jan;155(1):249-62. doi: 10.1210/en.2013-1657. Epub 2013 Dec 4.	Environmental toxicants such as perfluorooctanesulfonate (PFOS) have been implicated in male reproductive dysfunction, including reduced sperm count and semen quality, in humans. However, the underlying mechanism(s) remains unknown. Herein PFOS at 10-20 μM (~5-10 μg/mL) was found to be more potent than bisphenol A (100 μM) in perturbing the blood-testis barrier (BTB) function by disrupting the Sertoli cell tight junction-permeability barrier without detectable cytotoxicity. We also delineated the underlying molecular mechanism by which PFOS perturbed Sertoli cell BTB function using an in vitro model that mimics the BTB in vivo. First, PFOS perturbed F-actin organization in Sertoli cells, causing truncation of actin filaments at the BTB. Thus, the actin-based cytoskeleton was no longer capable of supporting the distribution and/or localization of actin-regulatory and adhesion proteins at the cell-cell interface necessary to maintain BTB integrity. Second, PFOS was found to perturb inter-Sertoli cell gap junction (GJ) communication based on a dye-transfer assay by down-regulating the expression of connexin-43, a GJ integral membrane protein. Third, phosphorylated focal adhesion kinase (FAK)-Tyr(407) was found to protect the BTB from the destructive effects of PFOS as shown in a study via an overexpression of an FAK Y407E phosphomimetic mutant. Also, transfection of Sertoli cells with an FAK-specific microRNA, miR-135b, to knock down the expression of phosphorylated FAK-Tyr(407) was found to worsen PFOS-mediated Sertoli cell tight junction disruption. In summary, PFOS-induced BTB disruption is mediated by down-regulating phosphorylated FAK-Tyr(407) and connexin-43, which in turn perturbed F-actin organization and GJ-based intercellular communication, leading to mislocalization of actin-regulatory and adhesion proteins at the BTB.				●						-		C	C
1295	実験動物（生殖発生毒性）	Wan, H T; Zhao, Y G; Wong, M H; Lee, K F; Yeung, W S B; Giesy, J P; Wong, C K C	Testicular signaling is the potential target of perfluorooctanesulfonate-mediated subfertility in male mice	2011	Biol Reprod. 2011 May;84(5):1016-23. doi: 10.1095/biolreprod.110.089219. Epub 2011 Jan 5.	Perfluorooctanesulfonate (PFOS) was produced and used by various industries and in consumer products. Because of its persistence, it is ubiquitous in air, water, soil, wildlife, and humans. Although the adverse effects of PFOS on male fertility have been reported, the underlying mechanisms have not yet been elucidated. Here, for the first time, the effects of PFOS on testicular signaling, such as gonadotropin, growth hormone, insulin-like growth factor, and inhibins/activins were shown to be directly related to male subfertility. Sexually mature 8-wk-old CD1 male mice were administered by gavages in corn oil daily with 0, 1, 5, or 10 mg/kg PFOS for 7, 14, or 21 days. Serum concentrations of testosterone and epididymal sperm counts were significantly lower in the mice after 21 days of the exposure to the highest dose compared with the controls. The expression levels of testicular receptors for gonadotropin, growth hormone, and insulin-like growth factor 1 were considerably reduced on Day 21 in mice exposed daily to 10 or 5 mg/kg PFOS. The transcript levels of the subunits of the testicular factors (i.e., inhibins and activins), Inha, Inhba, and Inhbb, were significantly lower on Day 21 of daily exposure to 10, 5, or 1 mg/kg PFOS. The mRNA expression levels of steroidogenic enzymes (i.e., StAR, CYP11A1, CYP17A1, 3beta-HSD, and 17beta-HSD) were notably reduced. Therefore, PFOS-elicited subfertility in male mice is manifested as progressive deterioration of testicular signaling.				●					●	-		C	C
1296	実験動物（生殖発生毒性）	Wolf, Cynthia J; Zehr, Robert D; Schmid, Judy E; Lau, Christopher; Abbott, Barbara D	Developmental effects of perfluorononanoic Acid in themouse are dependent on peroxisome proliferator-activated receptor-alpha	2010	PPAR Res. 2010;2010:282896. doi: 10.1155/2010/282896. Epub 2010 Sep 27.	Perfluorononanoic acid (PFNA) is one of the perfluoroalkyl acids found in the environment and in tissues of humans and wildlife. Prenatal exposure to PFNA negatively impacts survival and development of mice and activates the mouse and human peroxisome proliferator-activated receptor-alpha (PPARα). In the current study, we used PPARα knockout (KO) and 129S1/SvImJ wild-type (WT) mice to investigate the role of PPARα in mediating PFNA-induced in vivo effects. Pregnant KO and WT mice were dosed orally with water (vehicle control: 10 ml/kg), 0.83, 1.1, 1.5, or 2 mg/kg PFNA on gestational days (GDs) 1-18 (day of sperm plug = GD 0). Maternal weight gain, implantation, litter size, and pup weight at birth were unaffected in either strain. PFNA exposure reduced the number of live pups at birth and survival of offspring to weaning in the 1.1 and 2 mg/kg groups in WT. Eye opening was delayed (mean delay 2.1 days) and pup weight at weaning was reduced in WT pups at 2 mg/kg. These developmental endpoints were not affected in the KO. Relative liver weight was increased in a dose-dependent manner in dams and pups of the WT strain at all dose levels but only slightly increased in the highest dose group in the KO strain. In summary, PFNA altered liver weight of dams and pups, pup survival, body weight, and development in the WT, while only inducing a slight increase in relative liver weight of dams and pups at 2 mg/kg in KO mice. These results suggest that PPARα is an essential mediator of PFNA-induced developmental toxicity in the mouse.				●						-		C	C
1297	実験動物（生殖発生毒性）	York R.	Oral (gavage) developmental toxicity study of potassium perfluorobutane sulfonate (PFBS) in rats [sanitized]	2002	OPPTS. 870.3700 Prenatal development toxicity (teratology), 418-023A. Sponsor's Study Number: T-7485.12. Laboratory Project ID: Argus Research, Protocol Number: 418-023.	No abstract available				●					企業データ		D	D
1298	実験動物（生殖発生毒性）	York R.	Oral (gavage) dosage-range developmental toxicity study of potassium perfluorobutane sulfonate (PFBS) in rats	2003	Sponsor's Study Number: T-7485.11. Argus Research, Horsham, Pennsylvania.	No abstract available				●					企業データ		D	D
1299	実験動物（生殖発生毒性）	York R.	Oral (gavage) two-generation (one litter per generation) reproduction study of potassium perfluorobutane sulfonate (PFBS) in rats	2003	Sponsor's Study Number: T-7485.13. Argus Research, Horsham, Pennsylvania.	No abstract available				●					企業データ		D	D
1300	実験動物（生殖発生毒性）	Christian, M.S., Hoberman, A.M. and York, R.G.	combined oral (gavage) fertility, developmental and perinatal/postnatal reproduction toxicity study of pfos in rats	1999	Argus Research Laboratories, Inc., Horsham, PA U.S EPA. Docket 8EHQ-0200-00374.	No abstract available					●				U.S EPA. Docket 8EHQ-0200-00374.で検索したが入手不可		D	D
1301	実験動物（生殖発生毒性）	Gortner, E.G.	Oral teratology study of FC-95 in rats	1980	Safety Evaluation Laboratory and Riker Laboratories, Inc. Experiment Number: 0680TR0008, December.	No abstract available					●				企業データ		D	D

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献ランク①	文献ランク②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1302	実験動物（生殖発生毒性）	Grasty, R.C., Grey, B.E., Lau, C.S. and Rogers, J.M.	Window of susceptibility to perfluorooctane sulfonate (PFOS)-induced neonatal mortality in the rat	2003	Res. B Dev. Reprod. Toxicol., 67(5): 315. Meeting abstract.	The widely used perfluorinated chemical, PFOS, increases neonatal lethality in rodents following gestational exposure. We have previously demonstrated the critical window for this toxicity occurs between gestation days (GD) 17-20 in the rat. Here, we utilized a 2-day dosing regimen to further narrow the window of susceptibility. Timed-pregnant Sprague-Dawley rats were treated by oral gavage with 0, 25, or 50 mg/kg/d PFOS/K+ on GD 19-20. Maternal and neonatal toxicity paralleled those described previously. Dam weight gain was suppressed in both PFOS groups following dosing. Control dams gained 29 g over 2 days, whereas the high dose group lost 12 g. Litter size and pup weight on GD 21 were not different between groups. However, the number of live pups born was reduced in the 50 mg/kg group and average pup weight was significantly lower in both treatment groups. While no control pups died on postnatal day (PND) 0, the 25 and 50 mg PFOS/kg groups experienced 6 and 71% mortality, respectively, within the first 12 hours. Pup survival continued to be significantly lower in PFOS treated groups through PND 5, where the survival rates were 98, 66, and 3% for the 0, 25, and 50 mg/kg groups, respectively. Pup weight was also significantly reduced in the dosed groups on these days. Histological examination of lungs revealed differences in maturation between control and treated animals on PND 0. From these data, we conclude that exposure to PFOS on 2 days late in gestation is sufficient to induce 100% pup mortality and that PFOS-induced neonatal mortality may involve inhibition of perinatal lung maturation. This abstract does not reflect EPA policy.					●					-	1	A	A
1303	実験動物（生殖発生毒性）	Health Canada	Human health risk assessment for priority substances	1994	Minister of Supply and Services Canada, Ottawa, Ontario.	No abstract available					●					評価書		D	D
1304	実験動物（生殖発生毒性）	Liu, Li; Jin, Yi-He; Wang, Lie; Yu, Hong-Yao; Liu, Wei; Yu, Qi-Lin; Wang, Ke; Liu, Bing; Wang, Jing	Effects of perfluorooctane sulfonate on learning and memory of rat pups	2009	Zhonghua Yu Fang Yi Xue Za Zhi. 2009 Jul;43(7):622-7.	OBJECTIVE: To study the effects of prenatal and postnatal perfluorooctane sulfonate (PFOS) exposure on spatial learning and memory, N-methyl-D-aspartate receptor 2B (NR2B) mRNA and protein level in frontal cortex and hippocampus of rat pups and to explore the mechanism of developmental neurotoxicity induced by PFOS. METHODS: Twenty-eight pregnant rats were randomly divided into three groups in proportion of 3:2:2, including control group (C), low dose group (L) and high dose group (H) by means of randomized number table, which respectively received 0, 7.2, 14.4 mg/kg PFOS feed from pregnancy day 0 to postnatal day (PND) 30 by free feedings. The animal models of prenatal and postnatal non-exposure (CC), prenatal exposure (LC and HC), postnatal exposure (CL and CH), and prenatal and postnatal exposure (LL and HH) to PFOS were established by cross-fostering method. The spatial learning and memory were measured by water maze experiment,the NR2B mRNA levels in frontal cortex of rat pups was determined with semi-quantitative RT-PCR, NR2B protein express in cerebral cortex (frontal and temporal cortex) and hippocampus (CA1, CA3, CA4 and DG regions) of rat pups was detected by immunohistochemistry. RESULTS: The escape latency of CL, CH, LL and HH groups pups in water maze experiment were (99.83 +/- 25.77) s, (111.30 +/- 17.82) s, (106.40 +/- 18.71) s, (107.70 +/- 16.85) s, and longer as compared with CC group [(54.90 +/- 26.69) s] (q value were 4.349, 4.773, 6.026 and 5.641, respectively, P <0.01). The number of errors of HH group rat pups entering dead end was (22.30 +/- 7.56) at the training day 4, and it was significantly higher than that of CC group (9.80 +/- 4.64) (q = 5.173, P < 0.01). The NR2B mRNA levels of frontal cortex of pups in HC group at PND1, and LC group, HC group and HH group at PND14 were (0.167 +/- 0.008), (0.364 +/- 0.035), (0.341 +/- 0.030) and (0.328 +/- 0.045) respectively,which were significantly lower than CC group (0.271 +/- 0.060) and (0.465 +/- 0.067) (q values were 3.547, 3.739, 4.597 and 5.006, respectively, P< 0.05). The results of immunohistochemistry indicated that NR2B protein express of the hippocampus CA1 region of pups in LC group was (0.091 +/- 0.005), and showed significant lower than CC group which was (0.123 +/- 0.009) at PND1 (q = 5.209, P <0.05). At PND14, the effect of PFOS extended to cerebral cortex and hippocampus regions. At PND28, the effects of PFOS were showed in hippocampus CA1, CA3 and temporal cortex regions. CONCLUSION: Prenatal and postnatal exposure to PFOS should result in the spatial learning and memory damage,and the mechanism might be possibly involved in the decrease of NR2B level in cerebral cortex and hippocampal formation regions.					●					-		C	B
1305	実験動物（生殖発生毒性）	Liu, Xiaohui; Liu, Wei; Jin, Yihe; Yu, Wenguang; Wang, Faqi; Liu, Li	Effect of gestational and lactational exposure to perfluorooctanesulfonate on calcium-dependent signaling molecules gene expression in rats' hippocampus	2010	Arch Toxicol. 2010 Jan;84(1):71-9. doi: 10.1007/s00204-009-0467-2. Epub 2009 Sep 12.	Perfluorooctanesulfonate (PFOS) is an environmental contaminant found in human and animal tissues worldwide. The developing nervous system is thought to be particularly sensitive to PFOS by the fact that PFOS can cross blood-brain and placental barriers. Effect of gestational and lactational exposure to PFOS on central nervous system (CNS) in Wistar rats was investigated by the cross-foster model built with PFOS at 0 or 3.2 mg/kg food. Real-time reverse transcription-polymerase chain reaction was employed to evaluate the gene expression of calcium-dependent signaling molecules in rats' hippocampus which are critical to the function of CNS. The expression of calcium-related signaling molecules, such as N-methyl-D-aspartate receptor subtype-2B (NR2B), calmodulin (CaM), Ca2+/calmodulin-dependent kinase II alpha (CaMKIIalpha) and cAMP-response element-binding (CREB) were increased in the PFOS exposure group at postnatal day 1 (PND 1). The decreased NR2B in the prenatal PFOS exposure group, the decreased CaM in the pre-/postnatal PFOS exposure group, the increased CaMKIIalpha in the whole-life PFOS exposure group and the increased CREB in the prenatal/whole-life PFOS exposure group was observed at PND 7. At PND 35, rats exhibited the decreased NR2B in the pre-/postnatal and the whole-life PFOS exposure group, and the decreased CaM in the postnatal PFOS group. The results indicate that perinatal exposure to PFOS during the critical period of development of the brain may have neurotoxic effect on CNS by mediating the molecules of calcium signaling pathway.					●				●	-		C	B
1306	実験動物（生殖発生毒性）	Yahia, D., El-Nasser, M.A., Abedel-Latif, M., Tsukuba, C., Yoshida, M., Sato, I. et al.	Effects of perfluorooctanoic acid (PFOA) exposure to pregnant mice on reproduction	2010	JToxicol. Sci., 35(4): 527–533. doi: 10.2131/jts.35.527.	Perfluorooctanoic acid (PFOA) has similar characteristics to perfluorooctane sulfonate (PFOS) in reproduction toxicity featured by neonatal death. We found that PFOS exposure to mice during pregnancy led to intracranial blood vessel dilatation of fetuses accompanied by severe lung collapse which caused neonatal mortality. Thus, we adopted the corresponding experimental design to PFOS in order to characterize the neonatal death by PFOA. Pregnant ICR mice were given 1, 5 and 10 mg/kg PFOA daily by gavage from gestational day (GD) 0 to 17 and 18 for prenatal and postnatal evaluations, respectively. Five to nine dams per group were sacrificed on GD 18 for prenatal evaluation; other 10 dams were left to give birth. No maternal death was observed. The liver weight increased dose-dependently, with hepatocellular hypertrophy, necrosis, increased mitosis and mild calcification at 10 mg/kg. PFOA at 10 mg/kg increased serum enzyme activities (GGT, ALT, AST and ALP) with hypoproteinemia and hypolipidemia. PFOA treatment reduced the fetal body weight at 5 and 10 mg/kg. Teratological evaluation showed delayed ossification of the sternum and phalanges and delayed eruption of incisors at 10 mg/kg, but did not show intracranial blood vessel dilatation. Postnatal evaluation revealed that PFOA reduced the neonatal survival rate at 5 and 10 mg/kg. At 5 mg/kg pups were born alive and active and 16% died within 4 days observation, while all died within 6 hr after birth at 10 mg/kg without showing intracranial blood vessel dilatation. The cause of neonatal death by PFOA may be different from PFOS.						●				-		B	B
1307	実験動物（生殖発生毒性）	Bernard, Bruce K; Hoberman, Alan M; Brown, W Ray; Ranpuria, Anish K; Christian, Mildred S	Oral (gavage) two-generation (one litter per generation) reproduction study of ammonium perfluorooctanoic (APFO) in rats	2002	Int J Toxicol. 2002 Jul-Aug;21(4):301-18. doi: 10.1080/10915810290096469.	The potential for pentachlorophenol (penta) to induce general and reproductive/developmental toxicity was evaluated in Crl Sprague-Dawley rats, employing a two-generation reproduction toxicity study. Penta was administered by gavage at doses of 0, 10, 30, and 60 mg/kg/day. In both generations, the parental animals (30/sex/group) were intubated daily for 10 weeks before cohabitation and continuing through cohabitation, gestation, and lactation periods. Intubation of the F1 generation was begun 28 days postpartum. Animals were evaluated daily for mortality and general toxicity (clinical observations, body weights and gains, feed consumption). Organ weights were recorded and histopathological evaluations were made. Specific indices of reproductive function evaluated included estrous cycles, mating and fertility, parturition, lactation, viability, and growth and development of offspring, including sexual maturation, sperm parameters, and numbers of ovarian primordial follicles. All deaths in the parental rats were unrelated to penta. Expected metabolic effects of penta, sporadic increased liver weights associated with hepatocellular centrilobular hypertrophy and vacuolation and lipofuscin pigmentation, were evident in the 10-, 30-, and 60-mg/kg/day dose group P1 and F1 animals. Toxicity, in the form of liver pathology (single cell necrosis), reduced body weights and associated reductions in organ weights, and reduced feed consumption were noted in both generations at the 30- and 60-mg/kg/day doses. Developmental toxicity associated with these doses included reduced pup weights and viability. The 60-mg/kg/day dose also resulted in delayed sexual maturation, decreased spermatid counts, small prostates and testes, decreased implantations, reduced fertility, and increased resorptions of embryos. Based on these results, it was concluded that 30 mg/kg/day is the lowest-observable-adverse-effect level (LOAEL) and 10 mg/kg/day is the no-observable-adverse-effect level (NOAEL) for both reproductive and general toxicity. These findings are consistent with results from previously conducted studies wherein reproductive/developmental toxicity was observed only at doses that also induced general toxicity. It differs from previous findings in that the NOAEL for general toxicity is two to three times higher for the more pure product than for products produced and tested previously. In addition, the results did not indicate bioaccumulation of penta. Thus, penta did not selectively affect reproduction or development of the offspring of rats at a dose of 10 mg/kg/day, a dose that is 7000 to 20,000 times higher than human exposure.						●				-		C	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1308	実験動物（生殖発生毒性）	Liao, Chunyang; Wang, Thanh; Cui, Lin; Zhou, Qunfang; Duan, Shumin; Jiang, Guibin	Changes in synaptic transmission, calcium current, and neurite growth by perfluorinated compounds are dependent on the chain length and functional group	2009	Environ Sci Technol. 2009 Mar 15;43(6):2099-104. doi: 10.1021/es802985e.	Scientific and public concerns on perfluorinated compounds (PFCs) are increasingly growing because of their environmental persistency, bioaccumulation, and extensive distribution throughout the world. Little is known about the effects of PFCs on neural function and the underlying mechanisms. Recent evidence suggests that the toxicological effects of PFCs are closely correlated with their carbon chain lengths. In this present work, the actions of PFCs with varying chain length on cultured rat hippocampal neurons and possible action patterns were examined. Increases in the frequencies of spontaneous miniature postsynaptic current (mPSC) were commonly found in cultured neurons when perfused with PFCs. The increase of mPSC frequency was in proportion to the carbon chain length, and the potency of perfluorinated carboxylates was less pronounced than that of perfluorinated sulfonates. A comparable but less perceptible trend was also found for the amplitudes of voltage-dependent calcium current (I(Ca)). No regular change in pattern was observed for the effects of PFCs on activation and inactivation kinetics of I(Ca). Furthermore, prolonged treatment of PFCs inhibited the neurite growth of neuronsto various degrees. Comparisons between nonfluorinated and perfluorinated analogues demonstrated thatthefluorination in alkyl chain exerts stronger actions on neurons as compared to the surfactant activity. This study shows that PFCs exhibit adverse effects on cultured neurons to various extents, which is dependent on the carbon chain length and functional group attached to the fully fluorinated alkyl chain.									●	-		C	C
1309	実験動物（生殖発生毒性）	Thomford PJ	26-Week capsule toxicity study with ammonium perfluorooctanoate (APFO) in cynomolgus monkeys	2009	U.S. Environmental Protection Agency Administrative Record 226-1052a.	No abstract available						●			●	企業データ		D	D
1310	実験動物（生殖発生毒性）	Wang, F.; Liu, W.; Jin, Y.; Dai, J.; Yu, W.; Liu, X.; Liu, L.	Transcriptional effects of prenatal and neonatal exposure to PFOS in developing rat brain	2009	Environ Sci Technol. 44(5):1847–53. doi: 10.1021/es902799f.	Perfluorooctane sulfonate (PFOS), a persistent and bioaccumulative compound, is widely distributed in the environment. To explore the molecular mechanism of neonatal neurotoxic effects, we evaluated the transcriptional effects of prenatal and neonatal exposure to PFOS in developing rat brain by performing gene expression profiling in the cerebral cortex. Dams received 3.2 mg/kg PFOS in their feed from gestational day 1 (GD1) to weaning (PND 21). Pups then had free access to treated feed until PND 35 Six Illumina RatRef-12 Expression BeadChips were used to identify gene expression changes on postnatal days (PNDs) 1, 7, and 35 Significantly affected genes (P < 0.05) were involved in neuroactive ligand-receptor interaction, calcium signaling pathways, cell communication, long-term potentiation/depression, the cell cycle, and peroxisome proliferator-activated receptor (PPAR) signaling. To compare prenatal and lactational exposure contributions to transcriptional effects, a subset of altered genes obtained from the gene-profile study that represented neurobiological functions was analyzed using RT-PCR in a follow-up cross-foster study lasting from PND1 to 21 Prenatal and postnatal exposure to PFOS caused potential neurotoxicity as demonstrated by developmentally different global transcriptional changes. Prenatal exposure was more effective in altering expression of several genes. Also, transcriptional effects of PFOS exposure on neurodevelopment occurred primarily by disrupting the neuroendocrine system.									●	-		C	C
1311	実験動物（生殖発生毒性）	Wetzel LT	Rat teratology study, T-3351, final report	2009	US EPA AR-226 226-0014.	No abstract available									●	企業データ		D	D
1312	実験動物（発がん性）	Biegel, L. B.; Hurtt, M. E.; Frame, , S. R.; O'Connor, J. C.; Cook, J. C.	Mechanisms of extrahepatic tumor induction by peroxisome proliferators in male CD rats	2001	Toxicol Sci. 2001 Mar;60(1):44-55. doi: 10.1093/toxsci/60.1.44.	Wyeth-14,643 (WY) and ammonium perfluorooctanoate (C8) belong to a diverse class of compounds which have been shown to produce hepatic peroxisome proliferation in rodents. From previous work, WY, but not C8, has been shown to produce hepatocellular carcinoma in rats, while C8 has been shown to produce Leydig cell adenomas. In addition, based on a review of bioassay data a relationship appears to exist between peroxisome-proliferating compounds and Leydig cell adenoma and pancreatic acinar cell hyperplasia/adenocarinoma formation. To further investigate the relationship between peroxisome-proliferating compounds and hepatic, Leydig cell, and pancreatic acinar cell tumorigenesis, a 2-year feeding study in male CD rats was initiated to test the hypothesis that peroxisome proliferating compounds induce a tumor triad (liver, Leydig cell, pancreatic acinar cell), and to examine the potential mechanism for the Leydig cell tumors. The study was conducted using 50 ppm WY and 300 ppm C8. The concentration of WY in the diet was decreased to 25 ppm on test day 301 due to increased mortality. In addition to the ad libitum control, a second control was pair-fed to the C8 group. Interim sacrifices were performed at 1- or 3-month intervals. Peroxisome proliferation measured by β-oxidation activity and cell proliferation were measured in the liver and testis at all time points and in the pancreas beginning at the 9-month time point (cell proliferation only). Serum hormone concentrations (estradiol, testosterone, LH, FSH, and prolactin) were also measured at each time point. Increased relative liver weights and hepatic β-oxidation activity were observed in both the WY- and C8-treated rats at all time points. In contrast, hepatic cell proliferation was significantly increased only in the WY-treated group. Neither WY nor C8 significantly altered the rate of Leydig cell β-oxidation or Leydig cell proliferation when compared to the control groups. Moreover, the basal rate of β-oxidation in Leydig cells was approximately 20 times less than the rate of hepatic β-oxidation. There were no biologically meaningful differences in serum testosterone, FSH, prolactin, or LH concentrations in the WY- and C8-treated rats when compared to their respective controls. There were, however, significant increases in serum estradiol concentrations in the WY- and C8-treated rats at 1, 3, 6, 9, 15, 18, and 21 months. At 12 months, only the C8-treated rats had elevated serum estradiol concentrations when compared to the pair-fed control. Histopathological evaluation revealed compound-related increases in liver, Leydig cell, and pancreatic acinar cell tumors in both	●	●		●		●	●		●		1	A	
1313	実験動物（発がん性）	Butenhoff, J. L.; Chang, S. C.; Olsen, G. W.; Thomford, P. J.	Chronic dietary toxicity and carcinogenicity study with potassium perfluorooctanesulfonate in Sprague Dawley rats	2012	Toxicology. 2012 Mar 11;293(1-3):1-15. doi: 10.1016/j.tox.2012.01.003. Epub 2012 Jan 16.	To investigate toxicity and neoplastic potential from chronic exposure to perfluorooctanesulfonate (PFOS), a two-year toxicity and cancer bioassay was conducted with potassium PFOS (K$^+$ PFOS) in male and female Sprague Dawley rats via dietary exposure at nominal K$^+$ PFOS concentrations of 0, 0.5, 2, 5, and 20 μg/g (ppm) diet for up to 104 weeks. Additional groups were fed 20 ppm for the first 52 weeks, after which they were fed control diet through study termination (20 ppm Recovery groups). Scheduled interim sacrifices occurred on Weeks 4, 14, and 53, with terminal sacrifice between Weeks 103 and 106 K$^+$ PFOS appeared to be well-tolerated, with some reductions in body weight occurring in treated rats relative to controls over certain study periods. Male rats experienced a statistically significant decreased trend in mortality with significantly increased survival to term at the two highest treatment levels. Decreased serum total cholesterol, especially in males, and increased serum urea nitrogen were consistent clinical chemistry observations that were clearly related to treatment. The principal non-neoplastic effect associated with K$^+$ PFOS exposure was in livers of males and females and included hepatocellular hypertrophy, with proliferation of endoplasmic reticulum, vacuolation, and increased eosinophilic granulation of the cytoplasm. Statistically significant increases in hepatocellular adenoma were observed in males (p=0.046) and females (p=0.039) of the 20 ppm treatment group, and all of these tumors were observed in rats surviving to terminal sacrifice. The only hepatocellular carcinoma observed was in a 20 ppm dose group female. There were no treatment-related findings for thyroid tissue in rats fed K$^+$ PFOS through study termination; however, male rats in the 20 ppm Recovery group had statistically significantly increased thyroid follicular cell adenoma, which was considered spurious. There was no evidence of kidney or bladder effects. In rats, the dietary dose estimated as the lower 0.95 confidence limit of the benchmark dose for a 0.1 increase in hepatic tumors was 8 ppm for both sexes. Recent mechanistic studies suggest a PPARα/CAR/PXR-mediated mode of action for the liver tumors observed in the present two-year study.	●	●		●	●		●		●		1	A	
1314	実験動物（発がん性）	Butenhoff, J. L.; Kennedy, G. L.; Chang, S. C.; Olsen, G. W.	Chronic dietary toxicity and carcinogenicity study with ammonium perfluorooctanoate in Sprague-Dawley rats	2012	Toxicology. 2012 Aug 16;298(1-3):1-13. doi: 10.1016/j.tox.2012.04.001. Epub 2012 Apr 17.	In order to assess the potential chronic toxicity and tumorigenicity of ammonium perfluorooctanoate (APFO), a 2-year dietary study was conducted with male and female rats fed 30 ppm or 300 ppm (approximately 1.5 and 15 mg/kg). In males fed 300 ppm, mean body weights were lower across most of the test period and survival in these rats was greater than that seen either in the 30 ppm or the control group. Non-neoplastic effects were observed in liver in rats fed 300 ppm and included elevated liver weight, an increase in the incidence of diffuse hepatocellular hypertrophy, portal mononuclear cell infiltration, and mild hepatocellular vacuolation without an increase in hepatocellular necrosis. Mean serum activities of alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase were elevated up to three times the control means, primarily at the 300 ppm dose. A significant increase in Leydig cell tumors of the testes was seen in the males fed 300 ppm, and tumors of the liver and acinar pancreas, which are often observed in rats from chronic exposure to peroxisome proliferating agents, were not observed in this study. All other tumor types were those seen spontaneously in rats of this stock and age and were not associated with feeding of APFO.	●	●		●		●	●		●		1	A	
1315	in vitro（発がん性）	Li, ZR; Hromchak, R; Mudipalli, A; Bloch, A.	Tumor suppressor proteins as regulators of cell differentiation	2002	Cancer Res. 58: 4282-4287.	The products of the tumor suppressor genes are considered to function as specific inhibitors of tumor cell growth. In this communication, we present evidence to show that these proteins inhibit tumor cell proliferation by participating in the activation of tumor cell differentiation. The ML-1 human myeloblastic leukemia cells used in this study proliferate when treated with insulin-like growth factor I and transferrin but differentiate to monocytes when exposed to tumor necrosis factor or transforming growth factor ß1, or to macrophage-like cells when treated with both these cytokines. Initiation of proliferation but not of differentiation was followed by a 20- to 25-fold increase in the nuclear level of the DNA polymerase-associated processivity factor PCNA and of the proliferation-specific transcription factor E2F1. In contrast, induction of differentiation but not of proliferation was followed by a 25- to 30-fold increase in the nuclear level of the tumor suppressor proteins p53 (wild type), pRb, and p130/Rb2 and of the p53-dependent cyclin kinase inhibitor p21/Cip1. p53 and p21/Cip1, respectively, inhibit the expression and activation of PCNA, whereas p130 and pRb, respectively, inhibit the expression and activation of E2F1. As a result, G1-S-associated DNA and mRNA synthesis is inhibited, growth uncoupled from differentiation, and maturation enabled to proceed. Where this function of the tumor suppressor proteins is impaired, the capacity for differentiation is lost, which leads to the sustained proliferation that is characteristic of the cancer cell.	●	●								要確認		C	

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報抽出対象	文献ランク①	文献ランク②
1316	実験動物（発がん性）	NTP	NTP technical report on the toxicology and carcinogenesis studies of perfluorooctanoic acid (CASRN 335-67-1) administered in feed to Sprague Dawley (Hsd:Sprague Dawley SD) rats [NTP]	2020	NTP. (Technical Report 598). Research Triangle Park, NC.	No abstract available	●	●								NTP TR	1	A	
1317	実験動物（発がん性）	Thomford, P. J.	104-Week Dietary Chronic Toxicity and Carcinogenicity Study with Perfluorooctane Sulfonic Acid Potassium Salt (PFOS; T-6295) in Rats	2002	Covance Laboratories, Study No. 6329-183, 002148-002363	No abstract available	●	●		●			●		●	企業データ		A	
1318	実験動物（発がん性）	Benninghoff, Abby D; Orner, Gayle A; Buchner, Clarissa H; Hendricks, Jerry D; Duffy, Aaron M; Williams, David E	Promotion of hepatocarcinogenesis by perfluoroalkyl acids in rainbow trout	2012	Toxicol Sci. 2012 Jan;125(1):69-78. doi: 10.1093/toxsci/kfr267. Epub 2011 Oct 9.	Previously, we reported that perfluorooctanoic acid (PFOA) promotes liver cancer in a manner similar to that of 17β-estradiol (E2) in rainbow trout. Also, other perfluoroalkyl acids (PFAAs) are weakly estrogenic in trout and bind the trout liver estrogen receptor. The primary objective of this study was to determine whether multiple PFAAs enhance hepatic tumorigenesis in trout, an animal model that represents human insensitivity to peroxisome proliferation. A two-stage chemical carcinogenesis model was employed in trout to evaluate PFOA, perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluorooctane sulfonate (PFOS), and 8:2 fluorotelomer alcohol (8:2FtOH) as complete carcinogens or promoters of aflatoxin B(1) (AFB(1))- and/or N-methyl-N'-nitro-N-nitrosoguanidine (MNNG)-induced liver cancer. A custom trout DNA microarray was used to assess hepatic transcriptional response to these dietary treatments in comparison with E2 and the classic peroxisome proliferator, clofibrate (CLOF). Incidence, multiplicity, and size of liver tumors in trout fed diets containing E2, PFOA, PFNA, and PFDA were significantly higher compared with AFB(1)-initiated animals fed control diet, whereas PFOS caused a minor increase in liver tumor incidence. E2 and PFOA also enhanced MNNG-initiated hepatocarcinogenesis. Pearson correlation analyses, unsupervised hierarchical clustering, and principal components analyses showed that the hepatic gene expression profiles for E2 and PFOA, PFNA, PFDA, and PFOS were overall highly similar, though distinct patterns of gene treatment, particularly for PFNA. Overall, these data suggest that multiple PFAAs can promote liver cancer and that the mechanism of promotion may be similar to that of E2. expression were evident for each			●	●						要確認		C	
1319	実験動物（発がん性）	Klaunig, James E; Shinohara, Motoki; Iwai, Hiroyuki; Chengelis, Christopher P; Kirkpatrick, Jeannie B; Wang, Zemin; Bruner, Richard H	Evaluation of the chronic toxicity and carcinogenicity of perfluorohexanoic acid (PFHxA) in Sprague-Dawley rats	2015	Toxicol Pathol. 2015 Feb;43(2):209-20. doi: 10.1177/0192623314530532. Epub 2014 May 28.	Perfluorohexanoic acid (PFHxA), a 6-carbon perfluoroalkyl (C6; CAS # 307-24-4), has been proposed as a replacement for the commonly used 8-carbon perfluoroalkyls: perfluorooctanoic acid and perfluorooctane sulfonate. PFHxA is not currently a commercial product but rather the ultimate degradation product of C6 fluorotelomer used to make C6 fluorotelomer acrylate polymers. It can be expected that, to a greater or lesser extent, the environmental loading of PFHxA will increase, as C6 fluorotelomer acrylate treatments are used and waste is generated. This article reports on a chronic study (duration 104 weeks) that was performed to evaluate the possible toxicologic and carcinogenic effects of PFHxA in gavage (daily gavage, 7 days per week) treated male and female Sprague-Dawley (SD) rats. In the current study, dosage levels of 0, 2.5, 15, and 100 mg/kg/day of PFHxA (males) and 5, 30, and 200 mg/kg/day of PFHxA (females) were selected based on a previous subchronic investigation. No effects on body weights, food consumption, a functional observational battery, or motor activity were observed after exposure to PFHxA. While no difference in survival rates in males was seen, a dose-dependent decrease in survival in PFHxA-treated female rats was observed. Hematology and serum chemistry were unaffected by PFHxA. PFHxA-related histologic changes were noted in the kidneys of the 200-mg/kg/day group females. Finally, there was no evidence that PFHxA was tumorigenic in male or female SD rats at any of the dosage levels examined.			●	●							1	A	
1320	実験動物（発がん性）	3M	Two year oral (diet) toxicity/carcinogenicity study of fluorochemical FC-143 in rats	1983	Submitted to the U.S. Environmental Protection Agency under TSCA Section 8E. OTS0204926-1.	No abstract available				●		●			●	企業データ		A	
1321	実験動物（発がん性）	Abdellatif, A.; Al-Tonsy, A. H.; Awad, M. E.; Roberfroid, M.; Khan, M. N.	Peroxisomal enzymes and δ-hydroxydeoxyguanosine in rat liver treated with perfluorooctanoic acid	2003	Dis Markers. 2003;19(1):19-25. doi: 10.1155/2003/135859.	Although peroxisome proliferators are considered non-genotoxic agents, most of them, nevertheless, were found to promote and/or induce, hepatocellular carcinoma (HCC) in rodents. The aim of the present study is, first, to investigate whether the peroxisome proliferator perfluorooctanoic acid (PFOA) possesses inherent liver cancer promoting activity, and second, to study the possible mechanisms involved. To acheive these aims two protocols have been applied, a biphasic protocol (initiation by diethyl-nitrozamine (DEN) 200 mg/kg i.p. followed by treatment with 0.00005 or 0.0002 perflourooctanoic acid (PFOA) for 14 and 25 weeks) and a triphasic initiation, selection-promotion (IS) protocol (initiation by giving 200 mg/kg DEN i.p. followed by a selection procedure for 2 weeks consisting of giving 0.0003 2-acetylaminofluorene (2-AAF) in diet). In the middle of this treatment a single oral dose of carbon tetrachloride (2.0 ml/kg) was given, followed by giving diet containg 0.00015 of PFOA for 25 weeks. After applying both protocols, our results showed slight increase in the catalase activity while acyl CoA oxidase activity was markedly increased. Both experiments indicated that PFOA has a liver cancer promoting activity. Other groups of rats were given either basal diet or diet containing 0.0002 PFOA. Five or nine weeks later they were sacrificed and the levels of 8-hydroxydeoxyguanosine in the isolated DNA were estimated. The data showed a slight nonetheless insignificant increase in 8-hydroxydeoxyguanosine. From the present data, it is concluded that PFOA is a TRUE liver cancer promoter that may not require extensive initial DNA damage for its promoting activity.				●						要確認		B	
1322	実験動物（発がん性）	Corton, J Christopher; Cunningham, Michael L; Hummer, B Timothy; Lau, Christopher; Meek, Bette; Peters, Jeffrey M; Popp, James A; Rhomberg, Lorenz; Seed, Jennifer; Klaunig, James E	Mode of action framework analysis for receptor-mediated toxicity: The peroxisome proliferator-activated receptor alpha (PPARα) as a case study	2014	Crit Rev Toxicol. 2014 Jan;44(1):1-49. doi: 10.3109/10408444.2013.835784. Epub 2013 Nov 4.	Several therapeutic agents and industrial chemicals induce liver tumors in rodents through the activation of the peroxisome proliferator-activated receptor alpha (PPARα). The cellular and molecular events by which PPARα activators induce rodent hepatocarcinogenesis has been extensively studied and elucidated. This review summarizes the weight of evidence relevant to the hypothesized mode of action (MOA) for PPARα activator-induced rodent hepatocarcinogenesis and identifies gaps in our knowledge of this MOA. Chemical-specific and mechanistic data support concordance of temporal and dose-response relationships for the key events associated with many PPARα activators including a phthalate ester plasticizer di(2-ethylhexyl) phthalate (DEHP) and the drug gemfibrozil. While biologically plausible in humans, the hypothesized key events in the rodent MOA, for PPARα activators, are unlikely to induce liver tumors in humans because of toxicodynamic and biological differences in responses. This conclusion is based on minimal or no effects observed on growth pathways, hepatocellular proliferation and liver tumors in humans and/or species (including hamsters, guinea pigs and cynomolgous monkeys) that are more appropriate human surrogates than mice and rats at overlapping dose levels. Overall, the panel concluded that significant quantitative differences in PPARα activator-induced effects related to liver cancer formation exist between rodents and humans. On the basis of these quantitative differences, most of the workgroup felt that the rodent MOA is "not relevant to humans" with the remaining members concluding that the MOA is "unlikely to be relevant to humans". The two groups differed in their level of confidence based on perceived limitations of the quantitative and mechanistic knowledge of the species differences, which for some panel members strongly supports but cannot preclude the absence of effects under unlikely exposure scenarios.				●	●	●				要確認		C	
1323	実験動物（発がん性）	Hardisty, Jerry F; Willson, Gabrielle A; Brown, W Ray; McConnell, Ernest E; Frame, Steven R; Gaylor, David W; Kennedy, Gerald L; Butenhoff, John L	Pathology Working Group review and evaluation of proliferative lesions of mammary gland tissues in female rats fed ammonium perfluorooctanoate (APFO) in the diet for 2 years	2010	Drug Chem Toxicol. 2010 Apr;33(2):131-7. doi: 10.3109/01480541003667610.	Perfluorooctanoate (PFO) is a perfluorinated carboxylate that is widely distributed in the environment. A 2-year chronic study was conducted in rats fed either 30 or 300 ppm of ammonium perfluorooctanoate (APFO). To investigate the possible relationship of APFO exposure to proliferative mammary lesions, a Pathology Working Group (PWG) review of the original slides was performed. The consensus reached by the PWG was that the incidence of mammary-gland neoplasms was not affected by chronic dietary administration of APFO. Therefore, feeding female rats up to 300 ppm of APFO resulted in no increase in proliferative lesions of the mammary tissue.				●		●				要確認		B	

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ランク①	文献ランク②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1324	実験動物（発がん性）	Klaunig, James E; Babich, Michael A; Baetcke, Karl P; Cook, Jon C; Corton, J Chris; David, Raymond M; DeLuca, John G; Lai, David Y; McKee, Richard H; Peters, Jeffrey M; Roberts, Ruth A; Fenner-Crisp, Penelope A	PPARα agonist-induced rodent tumors: Modes of action and human relevance	2003	Crit Rev Toxicol. 2003;33(6):655-780. doi: 10.1080/713608372.	Widely varied chemicals--including certain herbicides, plasticizers, drugs, and natural products--induce peroxisome proliferation in rodent liver and other tissues. This phenomenon is characterized by increases in the volume density and fatty acid oxidation of these organelles, which contain hydrogen peroxide and fatty acid oxidation systems important in lipid metabolism. Research showing that some peroxisome proliferating chemicals are nongenotoxic animal carcinogens stimulated interest in developing mode of action (MOA) information to understand and explain the human relevance of animal tumors associated with these chemicals. Studies have demonstrated that a nuclear hormone receptor implicated in energy homeostasis, designated peroxisome proliferator-activated receptor alpha (PPARalpha), is an obligatory factor in peroxisome proliferation in rodent hepatocytes. This report provides an in-depth analysis of the state of the science on several topics critical to evaluating the relationship between the MOA for PPARalpha agonists and the human relevance of related animal tumors. Topics include a review of existing tumor bioassay data, data from animal and human sources relating to the MOA for PPARalpha agonists in several different tissues, and case studies on the potential human relevance of the animal MOA data. The summary of existing bioassay data discloses substantial species differences in response to peroxisome proliferators in vivo, with rodents more responsive than primates. Among the rat and mouse strains tested, both males and females develop tumors in response to exposure to a wide range of chemicals including DEHP and other phthalates, chlorinated paraffins, chlorinated solvents such as trichloroethylene and perchloroethylene, and certain pesticides and hypolipidemic pharmaceuticals. MOA data from three different rodent tissues--rat and mouse liver, rat pancreas, and rat testis--lead to several different postulated MOAs, some beginning with PPARalpha activation as a causal first step. For example, studies in rodent liver identified seven "key events," including three "causal events"--activation of PPARalpha, perturbation of cell proliferation and apoptosis, and selective clonal expansion--and a series of associative events involving peroxisome proliferation, hepatocyte oxidative stress, and Kupffer-cell-mediated events. Similar in-depth analysis for rat Leydig-cell tumors (LCTs) posits one MOA that begins with PPARalpha activation in the liver, but two possible pathways, one secondary to liver induction and the other direct inhibition of testicular testosterone biosynthesis. For this tumor, both proposed pathways involve changes in the metabolism and quantity of related hormones and hormone precursors. Key events in the postulated MOA for the third tumor type, pancreatic acinar-cell tumors (PACTs) in rats, also begin with PPARalpha activation in the liver, followed by changes in bile synthesis and composition. Using the new human relevance framework (HRF) (see companion article), case studies involving PPARalpha-related tumors in each of these three tissues produced a range of outcomes, depending partly on the quality and quantity of MOA data available from laboratory animals and related information from human data sources.				●						要確認			C
1325	実験動物（発がん性）	Klaunig, James E; Hocevar, Barbara A; Kamendulis, Lisa M	Mode of action analysis of perfluorooctanoic acid (PFOA) tumorigenicity and human relevance	2012	Reprod Toxicol. 2012 Jul;33(4):410-418. doi: 10.1016/j.reprotox.2011.10.014. Epub 2011 Nov 22.	Perfluorooctanoic acid (PFOA) is an environmentally persistent chemical used in the manufacturing of a wide array of industrial and commercial products. PFOA has been shown to induce tumors of the liver, testis and pancreas (tumor triad) in rats following chronic dietary administration. PFOA belongs to a group of compounds that are known to activate the PPARα receptor. The PPARα activation Mode of Action was initially addressed in 2003 [9] and further refined in subsequent reviews [92-94]. In the intervening time, additional information on PFOA effects as well as a further refinement of the Mode of Action framework warrants a re-examination of this compound for its cancer induction Mode of Action. This review will address the rodent (rat) cancer data and cancer Mode of Action of PFOA for tumors of the liver, testes and pancreas.				●		●				要確認			B
1326	実験動物（発がん性）	Nilsson, R; Beije, B; Préat, V; Erixon, K; Ramel, C	On the mechanism of the hepatocarcinogenicity of peroxisome proliferations	1991	Chem Biol Interact. 1991;78(2):235-50. doi: 10.1016/0009-2797(91)90017-2.	The absence of a genotoxic action in the rat of several peroxisome proliferators (PP) has been confirmed by measuring gross degradation, unscheduled DNA-synthesis (UDS), as well as by measurement of single strand breaks using alkali unwinding in absence and presence of inhibitors of DNA-repair. Similar results were obtained even after drastically lowering the glutathione content of liver. Further, after oral administration of ciprofibrate, no potentiating effect was found in vivo on the generation of micronuclei in hepatocytes by ionizing radiation. The metabolically inert PP, perfluorooctanoic acid, was found to act as a promoter of liver tumors in the rat induced by diethylnitrosamine in an initiation-selection-promotion protocol. The results are discussed in light of available information concerning the mechanism of action of PPs.				●						要確認			B
1327	実験動物（発がん性）	Ren, Hongzu; Vallanat, Beena; Nelson, David M; Yeung, Leo W Y; Guruge, Keerthi S; Lam, Paul K S; Lehman-McKeeman, Lois D; Corton, J Christopher	Evidence for the involvement of xenobiotic-responsive nuclear receptors in transcriptional effects upon perfluoroalkyl acid exposure in diverse species	2009	Reprod Toxicol. 2009 Jun;27(3-4):266-277. doi: 10.1016/j.reprotox.2008.12.011. Epub 2009 Jan 3.	Humans and ecological species have been found to have detectable body burdens of a number of perfluorinated alkyl acids (PFAA) including perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS). In mouse and rat liver these compounds elicit transcriptional and phenotypic effects similar to peroxisome proliferator chemicals (PPC) that work through the nuclear receptor peroxisome proliferator-activated receptor alpha (PPAR alpha). Recent studies indicate that along with PPAR alpha other nuclear receptors are required for transcriptional changes in the mouse liver after PFOA exposure including the constitutive activated receptor (CAR) and pregnane X receptor (PXR) that regulate xenobiotic metabolizing enzymes (XME). To determine the potential role of CAR/PXR in mediating effects of PFAAs in rat liver, we performed a meta-analysis of transcript profiles from published studies in which rats were exposed to PFOA or PFOS. We compared the profiles to those produced by exposure to prototypical activators of CAR, (phenobarbital (PB)), PXR (pregnenolone 16 alpha-carbonitrile (PCN)), or PPAR alpha (WY-14,643 (WY)). As expected, PFOA and PFOS elicited transcript profile signatures that included many known PPAR alpha target genes. Numerous XME genes were also altered by PFOA and PFOS but not WY. These genes exhibited expression changes shared with PB or PCN. Reexamination of the transcript profiles from the livers of chicken or fish exposed to PFAAs indicated that PPAR alpha, CAR, and PXR orthologs were not activated. Our results indicate that PFAAs under these experimental conditions activate PPAR alpha, CAR, and PXR in rats but not chicken and fish. Lastly, we discuss evidence that human populations with greater CAR expression have lower body burdens of PFAAs.				●						要確認			C
1328	実験動物（発がん性）	Eberhard Karbe, Roy L Kerlin	Cystic degeneration/spongiosis hepatis in rats	2002	Toxicol Pathol. ;30(2):216-27. doi: 10.1080/01926230275355955 1.	Cystic degeneration/spongiosis hepatis in rats has been proposed to be a preneoplastic and/or neoplastic lesion by some authors, because of its proliferative properties and persistent increased cell turnover rate in stop experiments using hepatocarcinogens, and the assumption that it can develop into a sarcoma. The neoplastic potential of cystic degeneration is questioned in this review article. Cystic degeneration, which appears to derive from altered Ito cells, does not have neoplastic histomorphologic characteristics, although it may be composed of cells with an increased mitotic index. In this regard, persistent proliferation is also seen with other nonneoplastic lesions. Arguments are presented to show that the induced, probably extremely rare sarcoma that was associated with cystic degeneration most likely derives from the very rare induced spherical Ito-cell aggregate with an unusually high cellular turnover rate in rats treated with hepatocarcinogens, and not from cystic degeneration. Also, in none of 12 referenced standard oncogenicity studies with chemically induced cystic degeneration was the lesion associated with mesenchymal (Ito-cell) tumors. Consequently, evidence is lacking that cystic degeneration in rats should be classified as a preneoplastic or neoplastic lesion. The 12 oncogenicity studies in rats with induced cystic degeneration showed a marked sex predilection, with males more likely to develop either spontaneous or chemically induced lesions. In these 12 studies, cystic degeneration was more often associated with hepatocellular hypertrophy or hepatotoxicity. rather than hepatocarcinogenicity. Thus, it is concluded that hepatocarcinogens induce cystic degeneration, not because they are carcinogenic. but because they have other effects on the liver, and that cystic degeneration may be a secondary/reparative change. Cystic degeneration in fish parallels the situation in rats in many respects, yet the existence of the lesion in other species, including man, is not as well supported. Based on the data presented in this review, spontaneous and induced cystic degeneration in rats and fish is not a preneoplastic or neoplastic lesion and risk assessment for man can be based on no-effect levels and safety margins, as for other nonneoplastic adverse effects that have no counterpart in man.					●					要確認			C
1329	実験動物（発がん性）	Sibinski, L.J.	Two-year oral (diet) toxicity/carcinogenicity study of fluorochemical FC-143 in rats. (Riker Experiment No. 0281CR0012)	1987	Vol 1–4. Riker Laboratories Inc./3M Company. St. Paul, Minnesota. 8 EHQ-1087-0394. Final Report, October 16, 1987. [cited in U.S. EPA (2005); EFSA (2008); OECD (2008)]	No abstract available						●			企業データ			A
1330	実験動物（発がん性）	NTP	NTP Technical report on the toxicology and carcinogenesis studies of perfluorooctanoic acid (CASRN 335-67-1) administered in feed to Sprague Dawley (Hsd:Sprague Dawly® SD®) Rats	2020	Natl Toxicol Program Tech Rep Ser. 2020 May;(598):NTP-TR-598. doi: 10.22427/NTP-TR-598.	Perfluorooctanoic acid (PFOA) is a perfluorinated alkyl substance (PFAS) with widespread exposure in the environment and human population. Lifetime exposure to this chemical is likely, which includes in utero and postnatal development. Previously conducted chronic carcinogenicity studies of PFOA began exposure after these critical periods of development, so it is unknown whether the carcinogenic response is altered if exposure during gestation and lactation is included. The current PFOA chronic studies were designed to assess the contribution of combined gestational and lactational exposure (herein referred to as perinatal exposure) to the chronic toxicity and carcinogenicity of PFOA. The hypothesis tested was that including exposure during gestation and lactation (perinatal exposure) with postweaning exposure would change the PFOA carcinogenic response quantitatively (more neoplasms) or qualitatively (different neoplasm types) compared to postweaning exposure alone. (Abstract Abridged).									●	1316と重複→削除予定			A

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献クラン①抽出	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1331	in vitro（PPAR）	Bijland, S.; Rensen, P. C. N.; Pieterman, E. J.; Maas, A. C. E.; van Der Hoorn, J. W.; van Erk, M. J.; Havekes, L. M.; Willems van Dijk, K.; Chang, S. C.; Ehresman, D. J.; Butenhoff, J. L.; Princen, H. M. G.	Perfluoroalkyl sulfonates cause alkyl chain length-dependent hepatic steatosis and hypolipidemia mainly by impairing lipoprotein production in APOE*3-Leiden CETP mice	2011	Toxicol Sci. 123: 290-303. doi: 10.1093/toxsci/kfr142. Epub 2011 Jun 24.	Perfluorobutane sulfonate (PFBS), perfluorohexane sulfonate (PFHxS), and perfluorooctane sulfonate (PFOS) are stable perfluoroalkyl sulfonate (PFAS) surfactants, and PFHxS and PFOS are frequently detected in human biomonitoring studies. Some epidemiological studies have shown modest positive correlations of serum PFOS with non-high-density lipoprotein (HDL)-cholesterol (C). This study investigated the mechanism underlying the effect of PFAS surfactants on lipoprotein metabolism. APOE*3-Leiden.CETP mice were fed a Western-type diet with PFBS, PFHxS, or PFOS (30, 6, and 3 mg/kg/day, respectively) for 44657 weeks. Whereas PFBS modestly reduced only plasma triglycerides (TG), PFHxS and PFOS markedly reduced TG, non-HDL-C, and HDL-C. The decrease in very low-density lipoprotein (VLDL) was caused by enhanced lipoprotein lipase-mediated VLDL-TG clearance and by decreased production of VLDL-TG and VLDL-apolipoprotein B. Reduced HDL production, related to decreased apolipoprotein AI synthesis, resulted in decreased HDL. PFHxS and PFOS increased liver weight and hepatic TG content. Hepatic gene expression profiling data indicated that these effects were the combined result of peroxisome proliferator-activated receptor alpha and pregnane X receptor activation. In conclusion, the potency of PFAS to affect lipoprotein metabolism increased with increasing alkyl chain length. PFHxS and PFOS reduce plasma TG and total cholesterol mainly by impairing lipoprotein production, implying that the reported positive correlations of serum PFOS and non-HDL-C are associative rather than causal.	●	●	●	●	●		●			-		B	B
1332	MOA（PPAR）	Elcombe, C. R.; Elcombe, B. M.; Foster, J. R.; Farrar, D. G.; Jung, R.; Chang, S. C.; Kennedy, G. L.; Butenhoff, J. L.	Hepatocellular hypertrophy and cell proliferation in Sprague-Dawley rats following dietary exposure to ammonium perfluorooctanoate occurs through increased activation of the xenosensor nuclear receptors PPARα and CAR/PXR	2010	Arch Toxicol. 84: 787-798. doi: 10.1007/s00204-010-0572-2. Epub 2010 Jul 8.	Ammonium perfluorooctanoate (APFO), a processing aid used in the production of fluoropolymers, produces hepatomegaly and hepatocellular hypertrophy in rodents. In mice, APFO-induced hepatomegaly is associated with increased activation of the xenosensor nuclear receptors, PPARα and CAR/PXR. Although non-genotoxic, chronic dietary treatment of Sprague-Dawley (S-D) rats with APFO produced an increase in benign tumours of the liver, acinar pancreas, and testicular Leydig cells. Most of the criteria for establishing a PPARα-mediated mode of action for the observed hepatocellular tumours have been previously established with the exception of the demonstration of increased hepatocellular proliferation. The present study evaluates the potential roles for APFO-induced activation of PPARα and CAR/PXR with respect to liver tumour production in the S-D rat and when compared to the specific PPARα agonist, 4-chloro-6-(2,3-xylidino)-2-pyrimidinylthioacetic acid (Wy 14,643). Male S-D rats were fed APFO (300 ppm in diet) or Wy 14643 (50 ppm in diet) for either 1, 7, or 28 days. Effects of treatment with APFO included: decreased body weight; hepatomegaly, hepatocellular hypertrophy, hepatocellular hyperplasia (microscopically and by BrdU labelling index), and hepatocellular glycogen loss; increased activation of PPARα (peroxisomal β-oxidation and microsomal CYP4A1 protein); decreased plasma triglycerides, cholesterol, and glucose; increased activation of CAR (CYP2B1/2 protein) and CAR/PXR (CYP3A1 protein). Responses to treatment with Wy 14643 were consistent with increased activation of PPARα, specifically: increased CYP4A1 and peroxisomal β-oxidation; increased hepatocellular hypertrophy and cell proliferation; decreased apoptosis; and hypolipidaemia. With the exception of decreased apoptosis, the effects observed with Wy 14643 were noted with APFO, and APFO was less potent. These data clearly demonstrate an early hepatocellular proliferative response to APFO treatment and suggest that the hepatomegaly and tumours observed after chronic dietary exposure of S-D rats to APFO likely are due to a proliferative response to combined activation of PPARα and CAR/PXR. This mode of action is unlikely to pose a human hepatocarcinogenic hazard.	●	●		●		●				-		B	B
1333	実験動物（肝毒性）	Erol, E; Kumar, LS; Cline, GW; Shulman, GI; Kelly, DP; Binas, B.	Liver fatty acid binding protein is required for high rates of hepatic fatty acid oxidation but not for the action of PPARalpha in fasting mice	2004	FASEB J. 18: 347-349. doi: 10.1096/fj.03-0330fje. Epub 2003 Dec 4.	Liver fatty acid binding protein (L-FABP) has been proposed to limit the availability of long-chain fatty acids (LCFA) for oxidation and for peroxisome proliferator-activated receptor alpha (PPAR-alpha), a fatty acid binding transcription factor that determines the capacity of hepatic fatty acid oxidation. Here, we used L-FABP null mice to test this hypothesis. Under fasting conditions, this mutation reduced beta-hydroxybutyrate (BHB) plasma levels as well as BHB release and palmitic acid oxidation by isolated hepatocytes. However, the capacity for ketogenesis was not reduced: BHB plasma levels were restored by octanoate injection; BHB production and palmitic acid oxidation were normal in liver homogenates; and hepatic expression of key PPAR-alpha target (MCAD, mitochondrial HMG CoA synthase, ACO, CYP4A3) and other (CPT1, LCAD) genes of mitochondrial and extramitochondrial LCFA oxidation and ketogenesis remained at wild-type levels. During standard diet, mitochondrial HMG CoA synthase mRNA was selectively reduced in L-FABP null liver. These results suggest that under fasting conditions, hepatic L-FABP contributes to hepatic LCFA oxidation and ketogenesis by a nontranscriptional mechanism, whereas L-FABP can activate ketogenic gene expression in fed mice. Thus, the mechanisms whereby L-FABP affects fatty acid oxidation may vary with physiological condition.	●	●								-		C	C
1334	実験動物（肝毒性）	Felter, S. P.; Foreman, J. E.; Boobis, A.; Corton, J. C.; Doi, A. M.; Flowers, L.; Goodman, J.; Haber, L. T.; Jacobs, A.; Klaunig, J. E.; Lynch, A. M.; Moggs, J.; Pandiri, A.	Human relevance of rodent liver tumors: key insights from a toxicology forum workshop on nongenotoxic modes of action	2018	Regul Toxicol Pharmacol. 92: 1-7. doi: 10.1016/j.yrtph.2017.11.003.	The Toxicology Forum sponsored a workshop in October 2016, on the human relevance of rodent liver tumors occurring via nongenotoxic modes of action (MOAs). The workshop focused on two nuclear receptor-mediated MOAs (Constitutive Androstane Receptor (CAR) and Peroxisome Proliferator Activated Receptor–alpha (PPARα), and on cytotoxicity. The goal of the meeting was to review the state of the science to -1 identify areas of consensus and differences, data gaps and research needs; -2 identify reasons for inconsistencies in current regulatory positions; and -3 consider what data are needed to demonstrate a specific MOA, and when additional research is needed to rule out alternative possibilities. Implications for quantitative risk assessment approaches were discussed, as were implications of not considering MOA and dose in hazard characterization and labeling schemes. Most, but not all, participants considered the CAR and PPARα MOAs as not relevant to humans based on quantitative and qualitative differences. In contrast, cytotoxicity is clearly relevant to humans, but a threshold applies. Questions remain for all three MOAs concerning what data are necessary to determine the MOA and to what extent it is necessary to exclude other MOAs.	●	●							●	-		D	C
1335	実験動物（肝毒性）	Guo, H.; Wang, J.; Yao, J.; Sun, S.; Sheng, N.; Zhang, X.; Guo, X.; Guo, Y.; Sun, Y.; Dai, J.	Comparative hepatotoxicity of novel PFOA alternatives (perfluoropolyether carboxylic acids) on male mice	2012	Environ Sci Technol. 53: 3929-3937. doi: 10.1021/acs.est.9b00148. Epub 2019 Mar 22.	As novel alternatives to perfluorooctanoic acid (PFOA), perfluoropolyether carboxylic acids (multiether PFECAs, CF3(OCF2) nCOO-, n = 2-4) have been detected in various environmental matrices; however, public information regarding their toxicities remains unavailable. To compare the hepatotoxicity of multiether PFECAs (e.g., PFO2HxA, PFO3OA, and PFO4DA) with PFOA, male mice were exposed to 0.4, 2, or 10 mg/kg/d of each chemical for 28 d, respectively. Results demonstrated that PFO2HxA and PFO3OA exposure did not induce marked increases in relative liver weight; whereas 2 and 10 mg/kg/d of PFO4DA significantly increased relative liver weight. Furthermore, PFO2HxA and PFO3OA demonstrated almost no accumulation in the liver or serum; whereas PFO4DA was accumulated but with weaker potential than PFOA. Exposure to 10 mg/kg/d of PFO4DA led to 198 differentially expressed liver genes (56 down-regulated, 142 up-regulated), with bioinformatics analysis highlighting the urea cycle disorder. Like PFOA, 10 mg/kg/d of PFO4DA decreased the urea cycle-related enzyme protein levels (e.g., carbamoyl phosphate synthetase 1) and serum ammonia content in a dose-dependent manner. Both PFOA and PFO4DA treatment (highest concentration) caused a decrease in glutamate content and increase in both glutamine synthetase activity and aquaporin protein levels in the brain. Thus, we concluded that PFO4DA caused hepatotoxicity, as	●	●								-		B	B
1336	実験動物（肝毒性）	Hall, A. P.; Elcombe, C. R.; Foster, J. R.; Harada, T.; Kaufmann, W.; Knippel, A.; Küttler, K.; Malarkey, D. E.; Maronpot, R. R.; Nishikawa, A.; Nolte, T.; Schulte, A.; Strauss, V.; York, M. J.	Liver hypertrophy: a review of adaptive (adverse and non-adverse) changes--conclusions from the 3rd International ESTP Expert Workshop [Review]	2012	Toxicol Pathol. 40: 971-994. doi: 10.1177/0192623312448935. Epub 2012 Jun 21.	Preclinical toxicity studies have demonstrated that exposure of laboratory animals to liver enzyme inducers during preclinical safety assessment results in a signature of toxicological changes characterized by an increase in liver weight, hepatocellular hypertrophy, cell proliferation, and, frequently in long-term (life-time) studies, hepatocarcinogenesis. Recent advances over the last decade have revealed that for many xenobiotics, these changes may be induced through a common mechanism of action involving activation of the nuclear hormone receptors CAR, PXR, or PPARα. The generation of genetically engineered mice that express altered versions of these nuclear hormone receptors, together with other avenues of investigation, have now demonstrated that sensitivity to many of these effects is rodent-specific. These data are consistent with the available epidemiological and empirical human evidence and lend support to the scientific opinion that these changes have little relevance to man. The ESTP therefore convened an international panel of experts to debate the evidence in order to more clearly define for toxicologic pathologists what is considered adverse in the context of hepatocellular hypertrophy. The results of this workshop concluded that hepatomegaly as a consequence of hepatocellular hypertrophy without histologic or clinical pathology alterations indicative of liver toxicity was considered an adaptive and a non-adverse reaction. This conclusion should normally be reached by an integrative weight of evidence approach.	●	●		●		●	●		●	-		D	C
1337	MOA（肝毒性）	Han, R.; Hu, M.; Zhong, Q.; Wan, C.; Liu, L.; Li, F.; Zhang, F.; Ding, W.	Effect of perfluorooctane sulphonate-induced Kupffer cell activation on hepatocyte proliferation through the NF-κB/TNF-α/IL-6-dependent pathway	2018	Chemosphere. 2018 Jun;200:283-294. doi: 10.1016/j.chemosphere.2018.02.137. Epub 2018 Feb 23.	Perfluorooctane sulphonate (PFOS) has been reported to accumulate in liver and cause damage. The molecular mechanism of the PFOS-induced hepatotoxicity has not been completely elucidated. The aim of the present study was to investigate whether PFOS-induced oxidative stress plays an important role in liver damage, and if so, what pathway it undergoes for the mechanism of its toxicological action. Male Sprague-Dawley (SD) rats were orally administrated with PFOS at single dose of 1 or 10 mg/kg body weight for 28 consecutive days. Increased serum levels of liver enzymes and abnormal ultra structural changes were observed in the PFOS-exposed rats. Particularly, PFOS exposure significantly increased intracellular reactive oxygen species (ROS) and nitric oxide (NO) production, but weakened intracellular antioxidant defence by inhibiting catalase and superoxide dismutase activities. Signal transduction studies showed that PFOS exposure significantly elevated inducible nitric oxide synthase (iNOS), Bax, cytochrome c, cleaved caspase-9 and cleaved caspase-3, indicating the mitochondria-dependent apoptotic pathway was activated. On the other hand, significant alterations of the PFOS-induced protein expression of NF-κB and IκBα in association with an enhanced level of TNF-α were observed. Taken together, these results indicate that mitochondria play an important role in PFOS-induced hepatotoxicity.	●	●	●							-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報対象抽出	文献ランク①	文献ランク②
1338	実験動物（肝毒性）	Liu, R. C.; Hurtt, M. E.; Cook, J. C.; Biegel, L. B.	Effect of the peroxisome proliferator, ammonium perfluorooctanoate (C8), on hepatic aromatase activity in adult male Crl:CD BR (CD) rats	1996	Fundam Appl Toxicol. 30: 220-228. doi: 10.1006/faat.1996.0059.	The incidence of Leydig cell adenomas increases in CD rats fed for 2 years with the hepatic peroxisome proliferator, ammonium perfluorooctanoate (C8). Treatment with C8 increased the serum concentration of estradiol in 2-week gavage studies, and feeding studies at various time points up to 2 years, and was also accompanied by increases in liver weight and hepatic beta-oxidation activity. Since peroxisome proliferators induce both hepatic beta-oxidation and specific cytochrome P450 enzymes, C8 may also induce aromatase (cytochrome P450-19A1), the cytochrome P450 monooxygenase which converts androgens to estrogens. This hypothesis was investigated in the present study. Adult male CD rats were dosed daily by gavage for 14 days with 0, 0.2, 2, 20, or 40 mg C8/kg body wt. An additional group, the pair-fed control, was fed at a rate matched to the daily consumption by the 40 mg C8/kg group. Treatment with C8 produced a dose dependent decrease in body weight, and increases in absolute and relative liver weights, and in the protein yield of hepatic microsomes. These C8-induced changes were associated with a 2-fold increase in the serum concentration of estradiol and up to a 16-fold increase in total hepatic aromatase activity. A significant linear correlation was established between serum estradiol and total hepatic aromatase activity. The absolute weights and the aromatase activity of the testes were not affected by C8. Hepatic peroxisomal beta-oxidation activity and the microsomal concentration of total cytochrome P450 were also increased by C8. A comparison of estimated EC50 values suggested that these parameters may be less sensitive to induction by C8 than hepatic aromatase activity. Co-incubation of control liver microsomes with C8 in the aromatase assay for 2 hr dose dependently reduced the apparent aromatase activity. This inhibition of aromatase in vitro but increase in vivo was further investigated using cultured rat hepatocytes. Decreases in aromatase activity were found after up to 42 hr of treatment with C8, but the enzyme activity was increased almost 2-fold after 66 hr. The results of this study suggest that the increased serum concentration of estradiol produced by C8 in rats is at least partly due to a direct effect on the liver to increase synthesis of estradiol through induction of aromatase cytochrome P450 in the endoplasmic reticulum.	●	●		●		●				-		B	B
1339	実験動物（肝毒性）	Minata, M.; Harada, K. H.; Kärrman, A.; Hitomi, T.; Hirosawa, M.; Murata, M.; Gonzalez, F. J.; Koizumi, A.	Role of peroxisome proliferator-activated receptor-alpha in hepatobiliary injury induced by ammonium perfluorooctanoate in mouse liver	2010	Ind Health. 2010;48(1):96-107. doi: 10.2486/indhealth.48.96.	Peroxisome proliferator-activated receptor-alpha (PPARalpha) has been suggested to protect against chemically induced hepatobiliary injuries in rodents. This function could mask the potential toxicities of perfluorooctanoic acid (PFOA) that is an emerging environmental contaminant and a weak ligand of PPARalpha. However its function has not been clarified. In this study, PFOA was found to elicit hepatocyte and bile duct injuries in Pparalpha-null mice after 4 wk treatment with PFOA ammonium salt (0, 12.5, 25, 50 micromol/kg/d, gavage). In wild-type mice, PFOA caused major hepatocellular damage dose-dependently and minor cholangiopathy observed only at 25 and 50 micromol/kg. In treated Pparalpha-null mice, PFOA produced marked fat accumulation, severe cholangiopathy, hepatocellular damage and apoptotic cells especially in bile ducts. Oxidative stress was also increased 4-fold at 50 micromol/kg and TNF-alpha mRNA was upregulated more than 3-fold at 25 micromol/kg in Pparalpha-null mice. Biliary bile acid/phospholipid ratios were higher in Pparalpha-null mice than in wild-type mice. Results from these studies suggest that PPARalpha is protective against PFOA and have a critical role in drug induced hepatobiliary injury.	●	●	●	●		●			●	-		B	B
1340	MOA（肝毒性）	Nakamura, T.; Ito, Y.; Yanagiba, Y.; Ramdhan, D. H.; Kono, Y.; Naito, H.; Hayashi, Y.; Li, Y.; Aoyama, T.; Gonzalez, F. J.; Nakajima, T.	Microgram-order ammonium perfluorooctanoate may activate mouse peroxisome proliferator-activated receptor alpha, but not human PPARalpha	2009	Toxicology. 265: 27-33. doi: 10.1016/j.tox.2009.09.004. Epub 2009 Sep 12.	Perfluorooctanoic acid (PFOA) is a ligand for peroxisome proliferator-activated receptor (PPAR) alpha, which exhibits marked species differences in expression and function, especially between rodents and humans. We investigated the functional difference in PFOA response between mice and humans, using a humanized PPARalpha transgenic mouse line. Three genotyped mice, 129/Sv wild-type (mPPARalpha), Pparalpha-null mice and humanized PPARalpha (hPPARalpha) mice (8-week-old males) were divided into three groups: the first was treated with water daily for 2 weeks by gavage (control group), and the remaining two groups were treated with 0.1 and 0.3mg/kg ammonium perfluorooctanate (APFO), respectively, for 2 weeks by gavage. The APFO dosages used did not influence the plasma triglyceride or total cholesterol levels in any mouse line, but the high dose increased both hepatic lipid levels only in mPPARalpha mice. APFO increased mRNA and/or protein levels of PPARalpha target genes cytochrome P450 Cyp4a10, peroxisomal thiolase and bifunctional protein only in the liver of mPPARalpha mice, but not in Pparalpha-null or hPPARalpha mice. This chemical also increased expression of mitochondrial very long chain acyl-CoA dehydrogenase only in the liver of mPPARalpha mice. Taken together, human PPARalpha may be less responsive to PFOA than that of mice when a relatively low dose is applied. This information may be very valuable in considering whether PFOA influences the lipid metabolism in humans.	●	●	●			●			●	-		B	B
1341	実験動物（肝毒性）	NTP	NTP technical report on the toxicity studies of perfluoroalkyl carboxylates (perfluorohexanoic acid, perfluorooctanoic acid, perfluorononanoic acid, and perfluorodecanoic acid) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats [NTP]	2019	NTP. (Toxicity Report 97). Research Triangle Park, NC.	No abstract available	●	●	●						●	NTP TR（No.1159と重複、削除予定）		D	
1342	実験動物（肝毒性）	Qazi, M. R.; Abedi, M. R.; Nelson, B. D.; Depierre, J. W.; Abedi-Valugerdi, M.	Dietary exposure to perfluorooctanoate or perfluorooctane sulfonate induces hypertrophy in centrilobular hepatocytes and alters the hepatic immune status in mice	2012	Int Immunopharmacol. 10: 1420-1427. doi: 10.1016/j.intimp.2010.08.009.	It is well established that exposure of mice to perfluorooctanoate (PFOA) or perfluorooctane sulfonate (PFOS) induces hepatomegaly and, concurrently, immunotoxicity. However, the effects of these perfluorochemicals on the histology and immune status of the liver have not been yet investigated and we have examined these issues here. Dietary treatment of male C57BL/6 mice with 0.00002 (w/w) PFOA or 0.00005 (w/w) PFOS for 10 days resulted in significant reductions in serum levels of cholesterol and triglycerides, a moderate increase in the serum activity of alkaline phosphatase (ALP) and hepatomegaly, without affecting other immune organs. This hepatomegaly was associated with marked hypertrophy of the centrilobular hepatocytes, with elevated numbers of cytoplasmic acidophilic granules and occasional mitosis. Furthermore, dietary exposure to PFOA or PFOS altered the hepatic immune status: whereas exposure to PFOA enhanced the numbers of total, as well as of phenotypically distinct subpopulations of intrahepatic immune cells (IHIC), and in particular the presumptive erythrocyte progenitor cells, treatment with PFOS enhanced only the numbers of hepatic cells that appear immunophenotypically to be erythrocyte progenitors, without affecting other types of IHIC. In addition, exposure to these compounds attenuated hepatic levels of tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ) and interleukin-4 (IL-4). Furthermore, the exposed animals exhibited a significant increase in hepatic levels of erythropoietin, a hormone required for erythropoiesis. Thus, in mice, PFOA- and PFOS-induced hepatomegaly is associated with significant alterations in hepatic histophysiology and immune status, as well as induction of hepatic erythropoiesis.	●	●		●	●					-		B	B
1343	実験動物（肝毒性）	U.S. EPA	Hepatocellular hypertrophy	2000	HED guidance document #G2002.01 [EPA Report]. Washington, DC.	No abstract available	●									評価書		D	
1344	実験動物（肝毒性）	Wan, C.; Han, R.; Liu, L.; Zhang, F.; Li, F.; Xiang, M.; Ding, W.	Role of miR-155 in fluorooctane sulfonate-induced oxidative hepatic damage via the Nrf2-dependent pathway	2016	Toxicol Appl Pharmacol. 2016 Mar 15;295:85-93. doi: 10.1016/j.taap.2016.01.023. Epub 2016 Feb 1.	Studies demonstrated that perfluorooctane sulfonate (PFOS) tends to accumulate in the liver and is capable to cause hepatomegaly. In the present study, we investigated the roles of miR-155 in PFOS-induced hepatotoxicity in SD rats and HepG2 cells. Male SD rats were orally administrated with PFOS at 1 or 10mg/kg/day for 28 days while HepG2 cells were treated with 0-50 μM of PFOS for 24h or 50 μM of PFOS for 1, 3, 6, 12 or 24h, respectively. We found that PFOS significantly increased the liver weight and serum alanine transaminase (ALT) and aspartate amino transferase (AST) levels in rats. Morphologically, PFOS caused actin filament remodeling and endothelial permeability changes in the liver. Moreover, PFOS triggered reactive oxygen species (ROS) generation and induced apoptosis in both in vivo and in vitro assays. Immunoblotting data showed that NF-E2-related factor-2 (Nrf2) expression and activation and its target genes were all suppressed by PFOS in the liver and HepG2 cells. However, PFOS significantly increased miR-155 expression. Further studies showed that pretreatment of HepG2 cells with catalase significantly decreased miR-155 expression and substantially increased Nrf2 expression and activation, resulting in reduction of PFOS-induced cytotoxicity and oxidative stress. Taken together, these results indicated that miR-155 plays an important role in the PFOS-induced hepatotoxicity by disrupting Nrf2/ARE signaling pathway.	●	●								-		B	B
1345	実験動物（肝毒性）	Wan, H. T.; Zhao, Y. G.; Wei, X.; Hui, K. Y.; Giesy, J. P.; Wong, C. K.	PFOS-induced hepatic steatosis, the mechanistic actions on β-oxidation and lipid transport	2012	Biochim Biophys Acta Gen Subj. 1820: 1092-1101. doi: 10.1016/j.bbagen.2012.03.010. Epub 2012 Mar 28.	BACKGROUND: Perfluorooctane sulfonate (PFOS) was produced by various industries and was widely used in diverse consumer products. Human sample analysis indicated PFOS contamination in body fluids. Animal studies revealed that PFOS tends to accumulate in livers and is able to induce hepatomegaly. However the underlying mechanism of PFOS-elicited hepatotoxicity has not yet been fully addressed. The objective of this study is to identify the cellular target of PFOS and to reveal the mechanisms of PFOS-induced toxicity.METHODS: In this study, mature 8-week old male CD-1 mice were administered 0, 1, 5 or 10 mg/kg/day PFOS for 3, 7, 14 or 21 days. Histological analysis of liver sections, and biochemical/molecular analysis of biomarkers for hepatic lipid metabolism were assessed.RESULTS: PFOS-induced steatosis was observed in a time- and dose-dependent manner. The gene expression levels of fatty acid translocase (FAT/CD36) and lipoprotein lipase (Lpl) were significantly increased by 10 and/or 5 mg/kg PFOS. Serum levels of very-low density lipoprotein were decreased by 14 days of PFOS exposure (p<0.05). The rate of mitochondrial β-oxidation was also found to be significantly reduced, leading to the restriction of fatty acid oxidation for energy production.CONCLUSION: Taken together, the disturbance of lipid metabolism leads to the accumulation of excessive fatty acids and triglycerides in hepatocytes.GENERAL SIGNIFICANCE: Since PFOS-elicited pathological manifestation resembles one of the most common human liver diseases-nonalcoholic fatty liver disease, environmental exposure to PFOS may attribute to the disease progression.	●	●					●		●	-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1346	実験動物（肝毒性）	Yan, S.; Wang, J.; Dai, J.	Activation of sterol regulatory element-binding proteins in mice exposed to perfluorooctanoic acid for 28 days	2015	Arch Toxicol. 89: 1569-1578. doi: 10.1007/s00204-014-1322-7. Epub 2014 Aug 6.	Perfluoroalkyl acids are widely used in numerous industrial and commercial applications due to their unique physical and chemical characteristics. Although perfluorooctanoic acid (PFOA) is associated with hepatomegaly through peroxisome proliferator-activated receptor α (PPARα) activation, liver fat accumulation and changes in gene expression related to fatty acid metabolism could still be found in PPARα-null mice exposed to PFOA. To explore the potential effects of PFOA on sterol regulatory element-binding proteins (SREBPs) activity, male mice were dosed with either Milli-Q water or PFOA at doses of 0.08, 0.31, 1.25, 5, and 20 mg/kg/day by gavage for 28 days. Liver total cholesterol concentrations and PFOA contents showed a dose-dependent decrease and increase, respectively. Transcriptional activity of PPARα and SREBPs was significantly enhanced in livers. Protein expression analyzed by Western blotting showed that PFOA exposure stimulated SREBP maturation. Furthermore, proteins blocked SREBP precursor transport, insulin-induced gene 1 (INSIG1) and INSIG2 proteins, as well as a protein-mediated nuclear SREBP proteolysis, F-box and WD-40 domain protein 7, decreased in mouse liver exposed to PFOA. The expression levels of the miR-183-96-182 cluster, which is possibly involved in a regulatory loop intermediated by SREBPs maturation, were also increased in the mouse liver after PFOA exposure. We also observed that PFOA induced lipid content and PPARα in Hepa 44567 cells after exposure to PFOA for 72 h but SREBPs were not activated in vitro. These results demonstrated that SREBPs were maturated by activating the miR-183-96-182 cluster-SREBP regulatory loop in PFOA-exposed mouse liver.	●	●							-		D	B
1347	実験動物（肝毒性）	Yan, Shengmin; Zhang, Hongxia; Guo, Xuejiang; Wang, Jianshe; Dai, Jiayin	High perfluorooctanoic acid exposure induces autophagy blockage and disturbs intracellular vesicle fusion in the liver	2017	Arch Toxicol. 2017 Jan;91(1):247-258. doi: 10.1007/s00204-016-1675-1. Epub 2016 Feb 15.	Perfluorooctanoic acid (PFOA) has been shown to cause hepatotoxicity and other toxicological effects. Though PPARα activation by PFOA in the liver has been well accepted as an important mechanism of PFOA-induced hepatotoxicity, several pieces of evidence have shown that the hepatotoxic effects of PFOA may not be fully explained by PPARα activation. In this study, we observed autophagosome accumulation in mouse livers as well as HepG2 cells after PFOA exposure. Further in vitro study revealed that the accumulation of autophagosomes was not caused by autophagic flux stimulation. In addition, we observed that PFOA exposure affected the proteolytic activity of HepG2 cells while significant dysfunction of lysosomes was not detected. Quantitative proteomic analysis of crude lysosomal fractions from HepG2 cells treated with PFOA revealed that 54 differentially expressed proteins were related to autophagy or vesicular trafficking and fusion. The proteomic results were further validated in the cells in vitro and livers in vivo after PFOA exposure, which implied potential dysfunction at the late stage of autophagy. However, in HepG2 cells, it seemed that further inhibition of autophagy did not significantly alter the effects of PFOA on cell viability. Although these findings demonstrate that PFOA blocked autophagy and disturbed intracellular vesicle fusion in the liver, the changes in autophagy were observed only at high cytotoxic concentrations of PFOA, suggesting that autophagy may not be a primary target or mode of toxicity. Furthermore, since altered liver autophagy was not observed at concentrations of PFOA associated with human exposures, the relevance of these findings must be questioned.	●	●							-		D	B
1348	実験動物（内分泌系）	Yu, Wen-Guang; Liu, Wei; Jin, Yi-He	Effects of perfluorooctane sulfonate on rat thyroid hormone biosynthesis and metabolism	2009	Environ Toxicol Chem. 2009 May;28(5):990-6. doi: 10.1897/08-345.1.	The potential toxicity of perfluorooctane sulfonate (PFOS), an environmentally persistent organic pollutant, is of great concern. The present study examines the ability of PFOS to disturb thyroid function and the possible mechanisms involved in PFOS-induced thyroid hormone alteration. Male Sprague-Dawley rats were exposed to 1.7, 5.0, and 15.0 mg/L of PFOS in drinking water for 91 consecutive days. Serum was collected for analysis of total and free thyroxine (T4), total triiodothyronine (T3), and thyrotrophin (TSH). Thyroid and liver were removed for the measurement of endpoints closely related to thyroid hormone biosynthesis and metabolism following PFOS exposure. Determined endpoints were the messenger RNA (mRNA) levels for two isoforms of uridine diphosphoglucuronosyl transferases (UGT1A6 and UGT1A1) and type 1 deiodinase (DIO1) in liver, sodium iodide symporter (NIS), TSH receptor (TSHR), and DIO1 in thyroid as well as the activity of thyroid peroxidase (TPO). Serum total T4 level decreased significantly at all applied dosages, whereas total T3 level increased markedly only at 1.7 mg/L of PFOS. No statistically significant toxic effects of PFOS on serum TSH were observed. Hepatic UGTIA1, but not UGT1A6, mRNA was up-regulated at 5.0 and 15.0 mg/L of PFOS. Treatment with PFOS lowered hepatic DIO1 mRNA at 15.0 mg/L but increased thyroidal DIO1 mRNA dose dependently. The activity of TPO, NIS, and TSHR mRNA in thyroid were unaffected by PFOS treatment. These results indicate that increased hepatic T4 glucuronidation via UGT1A1 and increased thyroidal conversion of T4 to T3 via DIO1 were responsible in part for PFOS-induced hypothyroxinemia in rats.	●	●	●	●					●	-		1	B	A
1349	MOA（肝毒性）	Zhang, Y.; Beesoon, S.; Zhu, L.; Martin, J. W.	Biomonitoring of perfluoroalkyl acids in human urine and estimates of biological half-life	2013	Environ Sci Technol. 2013 Sep 17;47(18):10619-27. doi: 10.1021/es401905e. Epub 2013 Aug 27.	Perfluoroalkyl acids (PFAAs) are persistent and bioaccumulative compounds that have been associated with adverse health outcomes. In human blood, PFAAs exist as both linear and branched isomers, yet for most linear homologues, and for all branched isomers, elimination rates are unknown. Paired blood and urine samples (n = 86) were collected from adults in China. They were analyzed by a sensitive isomer-specific method that permitted the detection of many PFAAs in human urine for the first time. For all PFAAs except perfluoroundecanoate (PFUnA), levels in urine correlated positively with levels in blood. Perfluoroalkyl carboxylates (PFCAs) were excreted more efficiently than perfluoroalkane sulfonates (PFSAs) of the same carbon chain-length. In general, shorter PFCAs were excreted more efficiently than longer ones, but for PFSAs, perfluorooctanesulfonate (PFOS, a C8 compound) was excreted more efficiently than perfluorohexanesulfonate (PFHxS, a C6 compound). Among PFOS and perfluorooctanoate (PFOA) isomers, major branched isomers were more efficiently excreted than the corresponding linear isomer. A one-compartment model was used to estimate the biological elimination half-lives of PFAAs. Among all PFAAs, the estimated arithmetic mean elimination half-lives ranged from 0.5 ± 0.1 years (for one branched PFOA isomer, 5m-PFOA) to 90 ± 11 years (for one branched PFOS isomer, 1m-PFOS). Urinary excretion was the major elimination route for short PFCAs (C ≤ 8), but for longer PFCAs, PFOS and PFHxS, other routes of excretion likely contribute to overall elimination. Urinary concentrations are good biomarkers of the internal dose, and this less invasive strategy can therefore be used in future epidemiological and biomonitoring studies. The very long half-lives of long-chain PFCAs, PFHxS, and PFOS isomers in humans stress the importance of global and domestic exposure mitigation strategies.	●	●	●	●		●			●	-			B	A
1350	in vitro（肝毒性）	Bjork, James A; Wallace, Kendall B	Structure-activity relationships and human relevance for perfluoroalkyl acid induced transcriptional activation of peroxisome proliferation in liver cell cultures	2009	Toxicol Sci. 2009 Sep;111(1):89-99. doi: 10.1093/toxsci/kfp093. Epub 2009 Apr 30.	Perfluoroalkyl acids (PFAAs) are widely distributed and environmentally persistent agents whose potential toxicity is not yet fully characterized. Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid elicit a number of potential toxicities in rodents, the most prevalent of which are governed by activation of the peroxisome proliferator-activated receptor alpha (PPARalpha). The purpose of this investigation was twofold: (1) To conduct a structure-activity relationship study of the transcriptional activation of peroxisome proliferation in primary rat liver cell cultures for PFAA-related carboxylic and sulfonic acids of varying carbon chain length and (2) to explore whether this activity can be translated to human liver cells in culture. Exposure to PFOA caused a dose-dependent stimulation of the expression of acyl-CoA oxidase (Acox), Cte/Acot1, and Cyp4a1/11 transcripts that are indicative of peroxisome proliferation in primary rat hepatocytes. PFOA concentrations of 30 microM and above caused cell injury characterized by the expression of Ddit3. Perfluorobutanoic acid (PFBA), on the other hand, stimulated Acox, Cte/Acot1, and Cyp4a1/11 gene expression in primary rat hepatocytes only at concentrations of 100 microM and above. Neither PFOA nor PFBA at concentrations up to 200 microM stimulated PPARalpha-related gene expression in either primary or HepG2 human liver cells. These data demonstrate that (1) PFFAs cause a concentration- and chain length-dependent increase in expression of gene targets related to cell injury and PPARalpha activation in primary rat hepatocytes, (2) the sulfonates are less potent than the corresponding carboxylates in stimulating PPARalpha-related gene expression in rat hepatocytes, and (3) stimulation of PPARalpha-mediated gene transcription is a mechanism that is not shared by human liver cells, adding further substantiation that PPARalpha-dependent liver toxicity in rodents does not extrapolate to assessing human health concerns.			●	●						-			B	B
1351	MOA（肝毒性）	Bjork, J A; Butenhoff, J L; Wallace, K B	Multiplicity of nuclear receptor activation by PFOA and PFOS in primary human and rodent hepatocytes	2011	Toxicology. 2011 Oct 9;288(1-3):8-17. doi: 10.1016/j.tox.2011.06.012. Epub 2011 Jun 23.	Perfluorooctanoate (PFOA) and perfluorooctanesulfonate (PFOS) are surface active fluorochemicals that, due to their exceptional stability to degradation, are persistent in the environment. Both PFOA and PFOS are eliminated slowly in humans, with geometric mean serum elimination half-lives estimated at 3.5 and 4.8 years, respectively. The biological activity of PFOA and PFOS in rodents is attributed primarily to transactivation of the nuclear receptor peroxisome proliferator activated receptor alpha (PPARA), which is an important regulator of lipid and carbohydrate metabolism. However, there are significant species-specific differences in the response to PFOA and PFOS exposure; non-rodent species, including humans, are refractory to several but not all of these effects. Many of the metabolic effects have been attributed to the activation of PPARA; however, recent studies using PPARα knockout mice demonstrate residual PPARA-independent effects, some of which may involve the activation of alternate nuclear receptors, including NR1I2 (PXR), NR1I3 (CAR), NR1H3 (LXRA), and NR1H4 (FXR). The objective of this investigation was to characterize the activation of multiple nuclear receptors and modulation of metabolic pathways associated with exposure to PFOA and PFOS, and to compare and contrast the effects between rat and human primary liver cells using quantitative reverse transcription PCR (RT-qPCR). Our results demonstrate that multiple nuclear receptors participate in the metabolic response to PFOA and PFOS exposure resulting in a substantial shift from carbohydrate metabolism to fatty acid oxidation and hepatic triglyceride accumulation in rat liver cells. This shift in intermediary metabolism was more pronounced for PFOA than PFOS. Furthermore, while there is some similarity in the activation of metabolic pathways between rat and humans, particularly in PPARA regulated responses; the changes in primary human cells were more subtle and possibly reflect an adaptive metabolic response rather than an overt metabolic regulation observed in rodents.			●	●						-			B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献ランク①	文献ランク②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1352	MOA（肝毒性）	Bojes, H K; Germolec, D R; Simeonova, P; Bruccoleri, A; Schoonhoven, R; Luster, M I; Thurman, R G	Antibodies to tumor necrosis factor alpha prevent increases in cell replication in liver due to the potent peroxisome proliferator WY14,643	1997	Carcinogenesis. 1997 Apr;18(4):669-74. doi: 10.1093/carcin/18.4.669.	Several structurally dissimilar hypolipidemic drugs, plasticizers and halogenated hydrocarbons induce peroxisomes in hepatocytes, and cause hepatocellular adenoma and carcinoma in rats and mice. The mechanism by which these agents act is unknown, although recent studies have suggested a link between increased cell proliferation and hepatic cancer caused by peroxisome proliferators. Here, we demonstrate that neutralizing antibodies to tumor necrosis factor alpha (TNF alpha) block increases in protein kinase C and cell proliferation due to [4-chloro-6-(2,3-xylidino)-2-pyrimidinylthio]acetic acid (WY-14,643), a hypolipidemic drug and potent peroxisome proliferator that causes tumors. WY-14,643 moderately elevated the level of TNF alpha mRNA in the liver. TNF alpha was detected immunohistochemically exclusively in Kupffer cells. These results demonstrate that WY-14,643 acts as an indirect mitogen on hepatocytes via TNF alpha. We propose that the Kupffer cell, a major source of TNF alpha in the liver, is involved in the mechanism of the mitogenic effect of WY-14,643.			●							-		D	C
1353	MOA（肝毒性）	Buhrke, Thorsten; Kibellus, Anja; Lampen, Alfonso	In vitro toxicological characterization of perfluorinated carboxylic acids with different carbon chain lengths	2013	Toxicol Lett. 2013 Apr 12;218(2):97-104. doi: 10.1016/j.toxlet.2013.01.025. Epub 2013 Feb 4.	Perfluorooctanoic acid (PFOA) is in use for the production of fluoropolymers (PFT). Due to its toxic properties it was proposed to replace the substance in its industrial applications by homologous compounds with shorter carbon chain length that were supposed to be less toxic compared to PFOA, however, the smaller PFOA homologs are poorly characterized so far. In this study we have conducted a comparative analysis of the toxicity of perfluorinated carboxylic acids (PFCA) with a carbon chain length ranging from four to twelve carbon atoms. By using the human hepatocarcinoma cell line HepG2 as an in vitro model for human hepatocytes we could show a positive correlation between the carbon chain length of the respective PFCA and its cytotoxicity. There was, however, no indication of an apoptotic mechanism for cytotoxicity. All PFCA under investigation were negative in two independent genotoxicity assays. As PFOA, being a well-known peroxisome proliferator, the other PFCA tested in this study were also shown to activate human peroxisome proliferator-activated receptor alpha (PPARα) with PFOA having the highest potential of PPARα activation. Moreover, the compounds showed weak potential to activate PPARγ and hardly activated PPARδ. Taken together, the in vitro study revealed that PFCA with a shorter carbon chain length seem to be less toxic than PFOA.			●						●	-		C	B
1354	MOA（肝毒性）	Bursch, W; Lauer, B; Timmermann-Trosiener, I; Barthel, G; Schuppler, J; Schulte-Hermann, R	Controlled death (apoptosis) of normal and putative preneoplastic cells in rat liver following withdrawal of tumor promoters	1984	Carcinogenesis. 1984 Apr;5(4):453-8. doi: 10.1093/carcin/5.4.453.	Numerous drugs, hormones and environmental pollutants induce liver growth by hypertrophy and/or hyperplasia, and promote preferential growth of putative preneoplastic foci in the liver. In the present study the regression of hyperplasia after cessation of inducer/promoter treatment was studied in normal liver and in liver foci. High doses of cyproterone acetate (CPA), a synthetic sex steroid, were administered to rats and produced a doubling of liver size; after cessation of treatment liver size declined, and 27% of the total liver DNA disappeared within 6 days. In histological sections from the involuting liver no necroses, but numerous apoptotic bodies (ABs) were found; retreatment with CPA interrupted the formation of ABs. These findings suggest that elimination of excess liver DNA after cessation of CPA treatment is due to controlled cell death by apoptosis. In a further series of experiments putative preneoplastic foci were produced by a single dose of N-nitrosomorpholine and subsequently stimulated to grow by 10 or 28 weeks of phenobarbital (PB) treatment. After withdrawal of PB numerous ABs were present in normal liver and in the foci; in both, retreatment with PB decreased the appearance of ABs. It appears that inhibition of cell death by PB may contribute to tumour promotion. Under all conditions tested more ABs were found in the foci than in non-focal parts of the liver, suggesting an enhanced cell turnover in foci. The apparent sensitivity of foci to mechanisms controlling cell death might eventually provide a means for elimination of preneoplastic lesions.			●							-		D	C
1355	MOA（肝毒性）	Calfee-Mason, Karen G; Spear, Brett T; Glauert, Howard P	Effects of vitamin E on the NF-kappaB pathway in rats treated with the peroxisome proliferator, ciprofibrate	2004	Toxicol Appl Pharmacol. 2004 Aug 15;199(1):1-9. doi: 10.1016/j.taap.2004.03.006.	Peroxisome proliferators (PPs) are a diverse group of nongenotoxic compounds, which induce hepatic tumors in rodents. The mechanisms leading to hepatic tumors have not been elucidated, but oxidative stress may play a role in the process. Previous studies in our laboratory have shown that peroxisome proliferators activate the transcription factor nuclear factor-kappa B (NF-kappaB) and that this activation is mediated at least in part by oxidative stress. We therefore hypothesized that increased dietary vitamin E would decrease NF-kappaB DNA binding in rodents treated with ciprofibrate (CIP). In this study, 36 male Sprague-Dawley rats were fed a purified diet containing varying levels of vitamin E (10, 50, 250 ppm alpha-tocopherol acetate). After 28 days on the purified diet, seven animals per vitamin E group received 0.01% CIP in the diet for 10 days. Electrophoretic mobility shift assays (EMSAs) showed that CIP treatment increased DNA binding of NF-kappaB. Increased dietary alpha-tocopherol acetate inhibited CIP-induced NF-kappaB DNA binding. Because NF-kappaB translocates to the nucleus upon the phosphorylation and degradation of inhibitor of IkappaB, we also used Western blots to measure cytosolic protein levels of IkappaBalpha and IkappaBbeta, and the IkappaB kinases, IKKalpha and IKKbeta. IkappaBalpha protein levels were decreased in all three CIP-treated groups, with the 10 ppm vitamin E diet also decreasing IkappaBalpha levels in control rats. No difference in IkappaBbeta protein levels was observed among any of the groups. The CIP-treated rats generally had lower protein levels of IKKalpha and IKKbeta. This study supports our working hypothesis that an increased antioxidant environment can inhibit CIP-mediated NF-kappaB induction.			●							-		D	C
1356	MOA（肝毒性）	Cheung, Connie; Akiyama, Taro E; Ward, Jerrold M; Nicol, Christopher J; Feigenbaum, Lionel; Vinson, Charles; Gonzalez, Frank J	Diminished hepatocellular proliferation in mice humanized for the nuclear receptor peroxisome proliferator-activated receptor alpha	2004	Cancer Res. 2004 Jun 1;64(11):3849-54. doi: 10.1158/0008-5472.CAN-04-0322.	Lipid-lowering fibrate drugs function as agonists for the nuclear receptor peroxisome proliferator-activated receptor alpha (PPARalpha). Sustained activation of PPARalpha leads to the development of liver tumors in rats and mice. However, humans appear to be resistant to the induction of peroxisome proliferation and the development of liver cancer by fibrate drugs. The molecular basis of this species difference is not known. To examine the mechanism determining species differences in peroxisome proliferator response between mice and humans, a PPARalpha-humanized mouse line was generated in which the human PPARalpha was expressed in liver under control of the tetracycline responsive regulatory system. The PPARalpha-humanized and wild-type mice responded to treatment with the potent PPARalpha ligand Wy-14643 as revealed by induction of genes encoding peroxisomal and mitochondrial fatty acid metabolizing enzymes and resultant decrease of serum triglycerides. However, surprisingly, only the wild-type mice and not the PPARalpha-humanized mice exhibited hepatocellular proliferation as revealed by elevation of cell cycle control genes, increased incorporation of 5-bromo-2'-deoxyuridine into hepatocyte nuclei, and hepatomegaly. These studies establish that following ligand activation, the PPARalpha-mediated pathways controlling lipid metabolism are independent from those controlling the cell proliferation pathways. These findings also suggest that structural differences between human and mouse PPARalpha are responsible for the differential susceptibility to the development of hepatocarcinomas observed after treatment with fibrates. The PPARalpha-humanized mice should serve as models for use in drug development and human risk assessment and to determine the mechanism of hepatocarcinogenesis of peroxisome proliferators.			●							-		D	C
1357	MOA（肝毒性）	Corton, J Christopher; Peters, Jeffrey M; Klaunig, James E	The PPARa-dependent rodent liver tumor response is not relevant to humans: addressing misconceptions	2018	Arch Toxicol. 2018 Jan;92(1):83-119. doi: 10.1007/s00204-017-2094-7. Epub 2017 Dec 2.	A number of industrial chemicals and therapeutic agents cause liver tumors in rats and mice by activating the nuclear receptor peroxisome proliferator-activated receptor α (PPARα). The molecular and cellular events by which PPARα activators induce rodent hepatocarcinogenesis have been extensively studied elucidating a number of consistent mechanistic changes linked to the increased incidence of liver neoplasms. The weight of evidence relevant to the hypothesized mode of action (MOA) for PPARα activator-induced rodent hepatocarcinogenesis is summarized here. Chemical-specific and mechanistic data support concordance of temporal and dose-response relationships for the key events associated with many PPARα activators. The key events (KE) identified in the MOA are PPARα activation (KE1), alteration in cell growth pathways (KE2), perturbation of hepatocyte growth and survival (KE3), and selective clonal expansion of preneoplastic foci cells (KE4), which leads to the apical event-increases in hepatocellular adenomas and carcinomas (KE5). In addition, a number of concurrent molecular and cellular events have been classified as modulating factors, because they potentially alter the ability of PPARα activators to increase rodent liver cancer while not being key events themselves. These modulating factors include increases in oxidative stress and activation of NF-kB. PPARα activators are unlikely to induce liver tumors in humans due to biological differences in the response of KEs downstream of PPARα activation. This conclusion is based on minimal or no effects observed on cell growth pathways and hepatocellular proliferation in human primary hepatocytes and absence of alteration in growth pathways, hepatocyte proliferation, and tumors in the livers of species (hamsters, guinea pigs and cynomolgus monkeys) that are more appropriate human surrogates than mice and rats at overlapping dose levels. Despite this overwhelming body of evidence and almost universal acceptance of the PPARα MOA and lack of human relevance, several reviews have selectively focused on specific studies that, as discussed, contradict the consensus opinion and suggest uncertainty. In the present review, we systematically address these most germane suggested weaknesses of the PPARα MOA.			●							-		D	C

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							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1358	MOA（肝毒性）	Doull, J; Cattley, R; Elcombe, C; Lake, B G; Swenberg, J; Wilkinson, C; Williams, G; van Gemert, M	Cancer risk assessment of di(2-ethylhexyl)phthalate: application of the new U	1999	Regul Toxicol Pharmacol. 1999 Jun;29(3):327-57. doi: 10.1006/rtph.1999.1296.	The current United States Environmental Protection Agency (EPA) classification of di(2-ethylhexyl)phthalate (DEHP) as a B2 "probable human" carcinogen is based on outdated information. New toxicology data and a considerable amount of new mechanistic evidence were used to reconsider the cancer classification of DEHP under EPA's proposed new cancer risk assessment guidelines. The total weight-of-evidence clearly indicates that DEHP is not genotoxic. In vivo administration of DEHP to rats and mice results in peroxisome proliferation in the liver, and there is strong evidence and scientific consensus that, in rodents, peroxisome proliferation is directly associated with the onset of liver cancer. Peroxisome proliferation is a transcription-mediated process that involves activation by the peroxisome proliferator of a nuclear receptor in rodent liver called the peroxisome proliferator-activated receptor (PPARalpha). The critical role of PPARalpha in peroxisomal proliferation and carcinogenicity in mice is clearly established by the lack of either response in mice genetically modified to remove the PPARalpha. Several mechanisms have been proposed to explain how, in rodents, peroxisome proliferation can lead to the formation of hepatocellular tumors. The general consensus of scientific opinion is that PPARalpha-induced mitogenesis and cell proliferation are probably the major mechanisms responsible for peroxisome proliferator-induced hepatocarcinogenesis in rodents. Oxidative stress appears to play a significant role in this increased cell proliferation. It triggers the release of TNFalpha by Kupffer cells, which in turn acts as a potent mitogen in hepatocytes. Rats and mice are uniquely responsive to the morphological, biochemical, and chronic carcinogenic effects of peroxisome proliferators, while guinea pigs, dogs, nonhuman primates, and humans are essentially nonresponsive or refractory; Syrian hamsters exhibit intermediate responsiveness. These differences are explained, in part, by marked interspecies variations in the expression of PPARalpha, with levels of expression in humans being only 1-10% of the levels found in rat and mouse liver. Recent studies of DEHP clearly indicate a nonlinear dose-response curve that strongly suggests the existence of a dose threshold below which tumors in rodents are not induced. Thus, the hepatocarcinogenic effects of DEHP in rodents result directly from the receptor-mediated, threshold-based mechanism of peroxisome proliferation, a well-understood process associated uniquely with rodents. Since humans are quite refractory to peroxisomal proliferation, even following exposure to potent proliferators such as hypolipidemic drugs, it is concluded that the hepatocarcinogenic response of rodents to DEHP is not relevant to human cancer risk at any anticipated exposure level. DEHP should be classified an unlikely human carcinogen with a margin of exposure (MOE) approach to risk assessment. The most appropriate and conservative point of reference for assessing MOEs should be 20 mg/kg/day, which is the mouse NOEL for peroxisome proliferation and increased liver weight. Exposure of the general human population to DEHP is approximately 30 microg/kg body wt/day, the major source being from residues in food. Higher exposures occur occupationally [up to about 700 microg/kg body wt/day (mainly by inhalation) based on current workplace standards] and through use of certain medical devices [e.g., up to 457 microg/kg body wt/day for hemodialysis patients (intravenous)], although these have little relevance because the routes of exposure bypass critical activation enzymes in the gastrointestinal tract.			●							-		C	C
1359	MOA（肝毒性）	Fang, Xuemei; Gao, Guizhen; Xue, Hongyu; Zhang, Xingtao; Wang, Haichao	In vitro and in vivo studies of the toxic effects of perfluorononanoic acid on rat hepatocytes and Kupffer cells	2012	Environ Toxicol Pharmacol. 2012 Sep;34(2):484-494. doi: 10.1016/j.etap.2012.06.011. Epub 2012 Jul 1.	This study investigated the toxic effects of perfluorononanoic acid (PFNA), a persistent organic pollutant, on rat hepatocytes and Kupffer cells in vitro and in vivo. The results showed that administration of 5μM PFNA increased the viabilities of the hepatocytes and the Kupffer cells. An exposure of 50μM PFNA did not alter the viabilities of both cells, as well as the release of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) from the primary cultured hepatocytes or the hepatocytes co-cultured with Kupffer cells. An exposure of 100μM PFNA only decreased the viability of the hepatocytes. The administration of PFNA changed the hepatocyte expression of several genes related to lipid metabolism in vitro and in vivo. Oil Red O Staining revealed that 5mg PFNA/kg/D treatment lead to dramatic accumulation of lipids in rat liver. At the same dose PFNA damaged hepatocytes histopathologically. Up-regulated expressions of the inflammatory cytokines occurred in the Kupffer cells treated with 50μM PFNA and in the livers of the rat receiving a 5mg PFNA/kg/D treatment. In addition, these cytokines also increased in serum of the rat receiving higher dose of PFNA. In summary, on the one hand, PFNA exposure affected the viability of the hepatocytes, hepatic lipid metabolism and lead to lipid accumulation in liver. On the other hand, for the first time, PFNA exposure was demonstrated to affect the viability of the Kupffer cells as well as their expression of cytokines, which involved in regulation of various liver functions. Therefore, we conclude that both the hepatocyte and the Kupffer cell contribute to the observed hepatotoxicity of PFNA.			●	●						-		C	C
1360	MOA（肝毒性）	Goll, V; Alexandre, E; Viollon-Abadie, C; Nicod, L; Jaeck, D; Richert, L	Comparison of the effects of various peroxisome proliferators on peroxisomal enzyme activities, DNA synthesis, and apoptosis in rat and human hepatocyte cultures	1999	Toxicol Appl Pharmacol. 1999 Oct 1;160(1):21-32. doi: 10.1006/taap.1999.8737.	Peroxisome proliferators (PPs) are a class of rodent nongenotoxic hepatocarcinogens that cause hepatocyte peroxisome proliferation, increased DNA synthesis, and decreased spontaneous apoptosis. We examined the effects of various PPs such as the hypolipidemic agents clofibric acid (CLO), bezafibrate (BEZA), ciprofibrate (CIPRO), and nafenopin (NAFE) and the plasticizer di-(2-ethylhexyl)phthalate (DEHP) on the various parameters in vitro in rat and human hepatocyte cultures. In rat hepatocyte cultures, after 72 h of treatment with the various PPs at 100-500 microM, a compound-dependent increase in acyl CoA oxidase (ACO) and carnitine acetyl transferase (CAT) activities, markers of peroxisome proliferation, was observed with the following potencies: CIPRO = NAFE > BEZA > CLO > DEHP. A minor (120-150%), but significant, no concentration-dependent increase in DNA synthesis and a marked, no compound-dependent and, with the exception of NAFE, no concentration-dependent 60-80% decrease in spontaneous apoptosis was observed with all tested compounds (50-250 microM) after 48 h of treatment. Inhibition of spontaneous apoptosis in PP-treated versus control rat hepatocyte cultures was also observed morphologically. Furthermore, PPs inhibited transforming growth factor beta (TGFbeta)-induced apoptosis but not tumor necrosis factor alpha (TNFalpha)/alpha Amanitine (alphaAma)-induced apoptosis in rat hepatocyte cultures. In human hepatocyte cultures, the various PPs at 50-500 microM did not affect peroxisomal enzyme activities, DNA synthesis, or spontaneous and induced (TGFbeta or TNFalpha/alphaAma) apoptosis. The compound-dependent peroxisome proliferation but no compound-dependent disruption of the mitogenic/apoptotic balance elicited by PPs in primary rat hepatocyte cultures supports the hypothesis that oxidative stress is directly linked to the hepatocarcinogenic potential of a given PP in rodents and that disruption of the mitogenic/apoptotic balance contributes to the development of PP-induced hepatocarcinogenesis. In addition, the absence of effects of all PPs on both peroxisome proliferation-associated parameters and mitogenic/apoptotic balance supports the hypothesis that human liver cells are refractory to PP-induced hepatocarcinogenesis.			●							-		C	C
1361	MOA（肝毒性）	Hasmall, S C; James, N H; Macdonald, N; West, D; Chevalier, S; Cosulich, S C; Roberts, R A	Suppression of apoptosis and induction of DNA synthesis in vitro by the phthalate plasticizers monoethylhexylphthalate (MEHP) and diisononylphthalate (DINP): a comparison of rat and human hepatocytes in vitro	1999	Arch Toxicol. 1999 Nov;73(8-9):451-6. doi: 10.1007/s002040050634.	Diethylhexylphthalate (DEHP) and diisononylphthalate (DINP) are plasticizers with many important commercial, industrial and medical applications. However, both DEHP and DINP are rodent peroxisome proliferators (PPs), a class of compounds that cause rodent liver tumours associated with peroxisome proliferation, induction of hepatic DNA synthesis and the suppression of apoptosis. Despite these effects in the rodent, humans appear to be nonresponsive to the adverse effects of PPs. Previously, we have shown that the fibrate hypolipidaemic peroxisome proliferator, nafenopin, induced DNA synthesis and suppressed apoptosis in rat but not in human hepatocytes. In this work, we have examined species differences in the response of rat and human hepatocytes to DEHP and DINP in vitro. In rat hepatocytes in vitro, both DINP and MEHP (a principle metabolite of DEHP and the proximal peroxisome proliferator) caused a concentration-dependent induction of DNA synthesis and suppression of both spontaneous and transforming growth factor beta1 (TGFbeta1)-induced apoptosis. Similarly, both MEHP and DINP caused a concentration-dependent induction of peroxisomal beta-oxidation although the response to DINP was less robust. In contrast to the pleiotropic response noted in rat hepatocytes, neither DINP nor MEHP caused an induction of beta-oxidation, stimulation of DNA synthesis and suppression of apoptosis in human hepatocytes cultured from three separate donors. These data provide evidence for species differences in the hepatic response to the phthalates DEHP and DINP, confirming that human hepatocytes appear to be refractory to the hepatocarcinogenic effects of PPs first noted in rodents.			●							-		C	C
1362	MOA（肝毒性）	Hasmall, S C; James, N H; Macdonald, N; Gonzalez, F J; Peters, J M; Roberts, R A	Suppression of mouse hepatocyte apoptosis by peroxisome proliferators: role of PPARa and TNFalpha	2000	Mutat Res. 2000 Mar 17;448(2):193-200. doi: 10.1016/s0027-5107(99)00236-5.	Peroxisome proliferators (PPs) are a diverse group of nongenotoxic chemicals that in rodents cause hepatic peroxisome proliferation, liver enlargement, increased replicative DNA synthesis and suppression of apoptosis. The effects of PPs in vivo can be reproduced in vitro where PPs can induce mouse hepatocyte DNA synthesis and suppress both spontaneous apoptosis and that induced by transforming growth factor beta (TGFbeta). In vitro, high concentrations (>500 U/ml) of exogenous tumour necrosis factor (TNFalpha) [M. Rolfe, N.H. James, R.A. Roberts, TNF suppresses apoptosis and induces S-phase in rodent hepatocytes: a mediator of the hepatocarcinogenicity of peroxisome proliferators?, Carcinogenesis 18 (1997) 2277-2280] are also able to stimulate hepatocyte DNA synthesis and suppress apoptosis, implicating TNFalpha in mediating or permitting the liver growth response to PPs. Here, using cultured mouse hepatocytes isolated from PPARalpha null mice, we have examined the role of the peroxisome proliferator activated receptor alpha (PPARalpha) in mediating the suppression of apoptosis caused by PPs. In addition we have investigated further the role of TNFalpha in mediating the rodent response to PPs. The PP nafenopin (50 microM) was unable to stimulate DNA synthesis measured by bromodeoxyuridine incorporation in these PPARalpha null mouse hepatocytes (96% of control), unlike epidermal growth factor, a growth factor used as a positive control. In assays of apoptosis using H33258 staining of chromatin condensation, nafenopin was unable to suppress either spontaneous or TGFbeta1-induced apoptosis. In contrast, high concentrations of TNFalpha (>500 U/ml) were able to both stimulate DNA synthesis (204% of control) and suppress apoptosis in PPARalpha null hepatocytes (40% and 38% of control for spontaneous and TGFbeta1-induced apoptosis respectively). However, TNFalpha could not stimulate beta-oxidation of palmitoyl CoA in either PPARalpha null mouse or B6C3F1 (PPARalpha wild type) mouse hepatocytes. These data confirm the dependence of the response to PPs on PPARalpha by demonstrating that PPARalpha mediates the suppression of hepatocyte apoptosis in response to PPs. In addition, the data provide evidence that high concentrations of TNFalpha can modulate DNA synthesis and apoptosis in the absence of PPs and PPARalpha. Thus, in vivo, physiological levels of TNFalpha may be permissive for a PPARalpha-dependent growth response to PPs.			●							-		C	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1363	MOA（肝毒性）	Hoivik, Debie J; Qualls, Charles W Jr; Mirabile, Rosanna C; Cariello, Neal F; Kimbrough, Carie L; Colton, Heidi M; Anderson, Steven P; Santostefano, Michael J; Morgan, Ronda J Ott; Dahl, Ray R; Brown, Alan R; Zhao, Zhiyang; Mudd, Paul N Jr; Oliver, William B Jr; Brown, H Roger; Miller, Richard T	Fibrates induce hepatic peroxisome and mitochondrial proliferation without overt evidence of cellular proliferation and oxidative stress in cynomolgus monkeys	2004	Carcinogenesis. 2004 Sep;25(9):1757-69. doi: 10.1093/carcin/bgh182. Epub 2004 May 6.	There is little primate risk factor data in the literature evaluating the relationship between proposed mechanisms of PPAR agonist-induced hepatocarcinogenesis at clinically relevant therapeutic exposures. These studies were conducted to characterize the hepatic effects of fenofibrate and ciprofibrate in the cynomolgus monkey. Male cynomolgus monkeys were given fenofibrate (250, 1250 or 2500 mg/kg/day) or ciprofibrate (3, 30, 150 or 400 mg/kg/day) for up to 15 days. The highest doses used were approximately 4 times (fenofibrate) and 9.4 times (ciprofibrate) the human therapeutic exposure for these agents based on AUC (area under the curve). For both compounds, there was a treatment-related increase in liver weight and periportal hepatocellular hypertrophy, which was related to increases in peroxisomes (up to 2.8 times controls) and mitochondria (up to 2.5 times controls). An increase in smooth endoplasmic reticulum probably contributed to the hypertrophy. There was no indication of cell proliferation as determined by the number of mitotic figures and this was confirmed by evaluating cell proliferation by immunohistochemical staining for the Ki-67 antigen. Consistent with the findings by light microscopy, there was no treatment-related effect on the level of mRNA for proteins known to be involved in the control of hepatocyte cell division or apoptosis (e.g. P21, Cyclin D1, PCNA, CDKN1A). Furthermore, there was minimal indication of oxidative stress. Thus, there was no evidence of lipofuscin accumulation, and there was no remarkable increase in the mRNA levels for most proteins known to respond to oxidative stress (e.g. catalase, glutathione peroxidase). A mild induction in the mRNA levels of cellular beta-oxidation and detoxification enzymes (e.g. acyl CoA oxidase, thioredoxin reductase) was observed. Collectively, the data from these studies suggest that the primate responds to PPARalpha agonists in a manner that is different from the rodent suggesting that the primate may be refractory to PPAR-induced hepatocarcinogenesis.			●							-		C	C
1364	MOA（肝毒性）	Holden, P R; Hasmall, S C; James, N H; West, D R; Brindle, R D; Gonzalez, F J; Peters, J M; Roberts, R A	Tumour necrosis factor a (TNFa): role in suppression of apoptosis by peroxisome proliferators	2000	Cell Mol Biol (Noisy-le-grand). 2000 Feb;46(1):29-39.	The peroxisome proliferator (PPs) class of non-genotoxic rodent hepatocarcinogens induce mouse hepatocyte DNA synthesis and suppress apoptosis. This phenotype can be reproduced in vitro using exogenous tumour necrosis factor alpha (TNFalpha), suggesting a role for TNFalpha in mediating the liver growth response to PPs. In hepatocytes isolated from the peroxisome proliferator activated receptor alpha (PPARalpha) null mouse, PPs are unable to stimulate DNA synthesis or to suppress either spontaneous or TGFbeta1-induced apoptosis. However, the ability of TNFalpha to modulate hepatocyte survival and growth is unaltered, suggesting that TNFalpha acts independently or downstream of PPARalpha to mediate the growth changes associated with PPARalpha activation. Since PPARalpha is a ligand activated transcription factor, we determined if TNFalpha gene expression was altered by PP treatment during an early time window preceding PP-induced growth changes. However there was no induction of TNFalpha expression by nafenopin over the constitutive levels noted in control cultured cells. In summary, TNFalpha acts downstream or independently of PPARalpha to mediate the suppression of apoptosis and induction of DNA synthesis by PPs. In this in vitro model, the PP nafenopin do not appear to mediate de novo TNFalpha gene expression suggesting that the response to nafenopin may be mediated by bioactivation or release of pre-existing TNFalpha protein from Kupffer cells.			●							-		C	C
1365	MOA（肝毒性）	Ito, Yuki; Yamanoshita, Osamu; Kurata, Yoshimasa; Kamijima, Michihiro; Aoyama, Toshifumi; Nakajima, Tamie	Induction of peroxisome proliferator-activated receptor alpha (PPARa)-related enzymes by di(2-ethylhexyl) phthalate (DEHP) treatment in mice and rats, but not marmosets	2007	Arch Toxicol. 2007 Mar;81(3):219-26. doi: 10.1007/s00204-006-0141-x. Epub 2006 Aug 26.	To clarify species differences in the induction of peroxisome proliferator-activated receptor alpha (PPARalpha)-related enzymes by di(2-ethylhexyl)phthalate (DEHP) exposure, we investigated the inductions of PPARalpha and its target genes (mitochondrial medium-chain acyl-CoA dehydrogenase (MCAD) and peroxisomal keto-acyl-CoA thiolase (PT) in liver from mice (CD-1), rats (Sprague-Dawley), and marmosets (Callithrix jacchus) exposed to DEHP. Male mice and rats were treated with 0, 1.25 and 2.5 mmol/kg DEHP for 2 weeks, and marmosets with 0, 0.25, 1.25 and 6.25 mmol/kg DEHP for 15 months by gavage. Hepatic mono(2-ethylhexyl)phthalate (MEHP) levels were significantly higher in mice and rats than in marmosets. The constitutive expression of hepatic PPARalpha was 5-7 times greater in rats and mice than in marmosets, but DEHP treatment did not induce PPARalpha-mRNA in all animals. The treatment-induced PT expression detected either by anti-PT antibody or PT-mRNA levels in the liver only from mice and rats, and the induction of the mRNA was greater in the latter than in the former. Thus, DEHP used in this experiment influenced the peroxisomal enzymes in mice and rats, but did not affect the mitochondrial enzymes in any animals or the peroxisomal enzymes in marmosets. These results suggest that there are species differences in the induction of PPARalpha-related enzymes, especially in peroxisomal enzymes by DEHP treatment, and their underlying mechanism may in part reside in the different constitutive levels of PPARalpha and different forming levels of MEHP.			●							-		C	C
1366	MOA（肝毒性）	James, N H; Soames, A R; Roberts, R A	Suppression of hepatocyte apoptosis and induction of DNA synthesis by the rat and mouse hepatocarcinogen diethylhexylphthalate (DEHP) and the mouse hepatocarcinogen 1,4-dichlorobenzene (DCB)	1998	Arch Toxicol. 1998 Dec;72(12):784-90. doi: 10.1007/s002040050574.	Nongenotoxic rodent hepatocarcinogens do not damage DNA but cause liver tumours in the rat and mouse, associated with the induction of hepatic DNA synthesis. Previously, we have demonstrated that nongenotoxic hepatocarcinogens such as phenobarbitone and the peroxisome proliferator (PP), nafenopin, also suppress rat hepatocyte apoptosis. The nongenotoxic chemicals 1,4-dichlorobenzene (DCB) and the PP, diethylhexyl phthalate (DEHP), both induce high levels of DNA synthesis in rat liver in vivo, but only DEHP is hepatocarcinogenic in this species. Here, we investigate whether the difference in rat carcinogenicity of these two hepatic mitogens may be due to differences in their ability to suppress hepatocyte apoptosis. In rat hepatocytes in vitro, MEHP (the active metabolite of DEHP) induced DNA synthesis 2.5-fold (P = 0.001) and suppressed 10- and 4-fold, respectively both spontaneous (P = 0.0008) and transforming growth factor beta1 (TGFbeta1)-induced (P = 0.0001) apoptosis. DCB gave a small (1.7-fold) increase in DNA synthesis (P = 0.03) and a small (1.7- to 2-fold) suppression of both spontaneous (P = 0.022) and TGFbeta1-induced (P = 0.015) apoptosis. We next analysed the induction of DNA synthesis and the suppression of apoptosis in rat liver in vivo. Both DEHP and DCB were able to induce DNA synthesis although, as seen in vitro, the induction by DCB (4.2-fold; P = 0.023) was less marked than that with DEHP (13.4-fold; P = 0.007). Similarly, DEHP and DCB were both able to suppress rat hepatocyte apoptosis in vivo but the magnitude of the suppression was comparable; apoptosis was reduced to undetectable levels in four out of five animals with DCB and three out of five with DEHP. Since both chemicals suppressed apoptosis and induced DNA synthesis in rat liver but, overall, DCB was less potent, the disparate hepatocarcinogenic potential of these two chemicals could arise from differences in the magnitude of growth perturbation. To test this hypothesis, we repeated the studies in mouse, a species where both DCB and DEHP are hepatocarcinogenic. Both in vitro and in vivo, DCB and DEHP/MEHP were able to suppress apoptosis and induce hepatocyte DNA synthesis in the mouse with comparable potencies. The data support the hypothesis that the carcinogenicity of nongenotoxic hepatocarcinogens is associated strongly with the ability to perturb hepatocyte growth regulation. However, the ability to effect such changes is not unique to nongenotoxic carcinogens and is common to some noncarcinogenic chemicals, such as DCB, suggesting that the growth perturbation may need to exceed a threshold for carcinogenesis.			●							-		C	C
1367	MOA（肝毒性）	Jolly, Robert A; Goldstein, Keith M; Wei, Tao; Gao, Hong; Chen, Peining; Huang, Shuguang; Colet, Jean-Marie; Ryan, Timothy P; Thomas, Craig E; Estrem, Shawn T	Pooling samples within microarray studies: a comparative analysis of rat liver transcription response to prototypical toxicants	2005	Physiol Genomics. 2005 Aug 11;22(3):346-55. doi: 10.1152/physiolgenomics.00260.2004. Epub 2005 May 24.	Combining or pooling individual samples when carrying out transcript profiling using microarrays is a fairly common means to reduce both the cost and complexity of data analysis. However, pooling does not allow for statistical comparison of changes between samples and can result in a loss of information. Because a rigorous comparison of the identified expression changes from the two approaches has not been reported, we compared the results for hepatic transcript profiles from pooled vs. individual samples. Hepatic transcript profiles from a single-dose time-course rat study in response to the prototypical toxicants clofibrate, diethylhexylphthalate, and valproic acid were evaluated. Approximately 50% more transcript expression changes were observed in the individual (statistical) analysis compared with the pooled analysis. While the majority of these changes were less than twofold in magnitude (approximately 80%), a substantial number were greater than twofold (approximately 20%). Transcript changes unique to the individual analysis were confirmed by quantitative RT-PCR, while all the changes unique to the pooled analysis did not confirm. The individual analysis identified more hits per biological pathway than the pooled approach. Many of the transcripts identified by the individual analysis were novel findings and may contribute to a better understanding of molecular mechanisms of these compounds. Furthermore, having individual animal data provided the opportunity to correlate changes in transcript expression to phenotypes (i.e., histology) observed in toxicology studies. The two approaches were similar when clustering methods were used despite the large difference in the absolute number of transcripts changed. In summary, pooling reduced resource requirements substantially, but the individual approach enabled statistical analysis that identified more gene expression changes to evaluate mechanisms of toxicity. An individual animal approach becomes more valuable when the overall expression response is subtle and/or when associating expression data to variable phenotypic responses.			●							-		D	C
1368	in vitro（PPAR）	Kawashima, H; Naganuma, T; Kusunose, E; Kono, T; Yasumoto, R; Sugimura, K; Kishimoto, T	Human fatty acid omegahydroxylase, CYP4A11: determination of complete genomic sequence and characterization of purified recombinant protein	2000	Arch Biochem Biophys. 2000 Jun 15;378(2):333-9. doi: 10.1006/abbi.2000.1831.	The gene of the human fatty acid omega-hydroxylase, CYP4A11, has been isolated from a human BAC library, and its complete genomic sequence has been determined. The CYP4A11 gene spanned 12,568 bp and contained 12 exons. The known PPAR recognition elements (PPRE), which were reported to be involved in the induction of CYP4A6 by clofibric acid, were not observed within the 5'-flanking region of the CYP4A11 gene. The recombinant CYP4A11 protein expressed in Escherichia coli using the pCWOri expression vector was purified to an almost electrophoretically homogeneous state with a specific content of 6.4 nmol of P450/mg of protein. This P450 exhibited omega-hydroxylation activity toward laurate, with a turnover number of 14.7 nmol/min/nmol of P450. The apparent K(m) and V(max) values were 56.7 microM and 15.2 nmol/min/nmol of P450, respectively. It also showed omega-hydroxylation activity toward palmitate, with a turnover number of 0.78 nmol/min/nmol of P450. Although several reports from other groups described that CYP4A11 preparations catalyzed omega-hydroxylation of arachidonic acid, our purified recombinant protein exhibited no activity toward arachidonic acid nor prostaglandin A(1).			●							-		C	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ラン①①	文献ラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1369	in vitro（PPAR）	Kersten, Sander; Stienstra, Rinke	The role and regulation of the peroxisome proliferator activated receptor alpha in human liver	2017	Biochimie. 2017 May;136:75-84. doi: 10.1016/j.biochi.2016.12.019. Epub 2017 Jan 8.	The peroxisome proliferator-activated receptor α (PPARα) is a ligand-activated transcription factor that is abundantly expressed in liver. PPARα is activated by fatty acids and various other lipid species, as well as by a class of chemicals referred to as peroxisome proliferators. Studies in mice have shown that PPARα serves as the master regulator of hepatic lipid metabolism during fasting. In addition, PPARα suppresses inflammation and the acute phase response. Comparatively little is known about PPARα in human liver. Here, an overview is provided of the role and regulation of PPARα in human liver. The main outcomes are: 1) the level of PPARA mRNA expression in human and mouse liver is similar. 2) Expression of PPARA in human liver is reduced in patients with non-alcoholic steatohepatitis or infected with the hepatitis C virus. 3) PPARα in human liver is able to effectively induce the expression of numerous genes involved in numerous lipid metabolic pathways, including microsomal, peroxisomal and mitochondrial fatty acid oxidation, fatty acid binding and activation, fatty acid elongation and desaturation, synthesis and breakdown of triglycerides and lipid droplets, lipoprotein metabolism, gluconeogenesis, bile acid metabolism, and various other metabolic pathways and genes. 4) PPARα activation in human liver causes the down-regulation of a large number of genes involved in various immunity-related pathways. 5) Peroxisome proliferators do not promote tumour formation in human liver as opposed to mouse liver because of structural and functional differences between human and mouse PPARα. 6) In addition to helping to correct dyslipidemia, PPARα agonists may hold promise as a therapy for patients with cholestatic liver diseases, non-alcoholic fatty liver disease, and/or type 2 diabetes.			●							-		C	C
1370	MOA（肝毒性）	Kurata, Y; Kidachi, F; Yokoyama, M; Toyota, N; Tsuchitani, M; Katoh, M	Subchronic toxicity of di(2- ethylhexyl)phthalate in common marmosets: lack of hepatic peroxisome proliferation, testicular atrophy, or pancreatic acinar cell hyperplasia	1998	Toxicol Sci. 1998 Mar;42(1):49-56. doi: 10.1006/toxs.1997.2414.	To evaluate the toxicological effect, di(2-ethylhexyl)phthalate (DEHP) was administered orally at 100, 500, and 2500 mg/kg to four male and four female marmosets in each group for 13 weeks. Its potentials of hepatic peroxisome proliferation, testicular atrophy, and pancreatic acinar cell hyperplasia were evaluated more closely. Clofibrate, which potently causes peroxisome proliferation in rodents, was administered in like manner at 250 mg/kg as a reference drug. DEHP induced significant suppression of weight gain in males at 2500 mg/kg. However, the increase in liver mass and hypertrophy of hepatocytes were not detected in organ weight measurements or histopathological examination. The number of peroxisomes, volume density, peroxisome morphology, and peroxisomal enzyme activities were not different from those in the control group, though the males treated with 500 and 2500 mg/kg DEHP showed 1.3- and 1.4-fold increases in mean peroxisome volume, respectively. In contrast, clofibrate induced 2.2 (in male)- and 1.9-fold (in female) increases in hepatic cyanide-insensitive acyl CoA oxidation system activity, 1. 2 (in male)- and 1.7-fold (in female) increases in hepatic carnitine-dependent acetyltransferase activity, and 1.8 (in male)- and 3.0-fold (in female) increases of carnitine-dependent palmitoyltransferase activity. Cytochrome P-450 contents tended to increase in all males and females administered 500 and 2500 mg/kg of DEHP and clofibrate associated with the increase in hepatic microsomal protein content, suggesting a relationship with the treatment. The atrophic change in the testis or proliferative change in the pancreatic acinar cells seen in rodents were not seen histopathologically; also, no changes were observed in testes weight, testicular zinc level, blood levels of testosterone and estradiol, pancreas weight, and blood levels of cholecystokinin. Finally, no changes considered to be due to the administration of DEHP were noted in blood chemical examination or pathological examination of other organs.			●							-		C	C
1371	MOA（肝毒性）	Lee, S S; Pineau, T; Drago, J; Lee, E J; Owens, J W; Kroetz, D L; Fernandez-Salguero, P M; Westphal, H; Gonzalez, F J	Targeted disruption of the alpha isoform of the peroxisome proliferator-activated receptor gene in mice results in abolishment of the pleiotropic effects of peroxisome proliferators	1995	Mol Cell Biol. 1995 Jun;15(6):3012-22. doi: 10.1128/MCB.15.6.3012.	To gain insight into the function of peroxisome proliferator-activated receptor (PPAR) isoforms in rodents, we disrupted the ligand-binding domain of the alpha isoform of mouse PPAR (mPPAR alpha) by homologous recombination. Mice homozygous for the mutation lack expression of mPPAR alpha protein and yet are viable and fertile and exhibit no detectable gross phenotypic defects. Remarkably, these animals do not display the peroxisome proliferator pleiotropic response when challenged with the classical peroxisome proliferators, clofibrate and Wy-14,643. Following exposure to these chemicals, hepatomegaly, peroxisome proliferation, and transcriptional-activation of target genes were not observed. These results clearly demonstrate that mPPAR alpha is the major isoform required for mediating the pleiotropic response resulting from the actions of peroxisome proliferators. mPPAR alpha-deficient animals should prove useful to further investigate the role of this receptor in hepatocarcinogenesis, fatty acid metabolism, and cell cycle regulation.			●							-		C	C
1372	MOA（肝毒性）	Li, Chuan-Hai; Ren, Xiao-Min; Cao, Lin-Ying; Qin, Wei-Ping; Guo, Liang-Hong	Investigation of binding and activity of perfluoroalkyl substances to the human peroxisome proliferator-activated receptor b/d	2019	Environ Sci Process Impacts. 2019 Nov 1;21(11):1908-1914. doi: 10.1039/c9em00218a. Epub 2019 Jul 23.	Previously, perfluoroalkyl substances (PFASs) have been found to be associated with many adverse effects mediated by the peroxisome proliferator-activated receptor α (PPARα) and PPARγ. Here, we found another subtype of the peroxisome proliferator-activated receptors (PPARs); the PPARβ/δ mediated pathway might also be a potential adverse outcome pathway for PFASs. We investigated the direct binding and transcriptional activity of PFASs toward human PPARβ/δ, and further revealed the structure-binding and structure-activity relationship between PFASs and PPARβ/δ. The receptor binding experiment showed that their binding potency was dependent on the carbon chain length and the terminal functional group. For twelve perfluoroalkyl carboxylic acids (PFCAs), an inverted U-shaped relationship existed between the PPARβ/δ binding potency and the carbon chain length, with perfluorododecanoc acid (C12) showing the highest binding potency. The three perfluoroalkane sulfonic acids (PFSAs) exhibited a stronger binding potency than their PFCA counterparts. The two fluorotelomer alcohols (FTOHs) showed no binding potency. In receptor transcriptional activity assays, they enhanced the PPARβ/δ transcriptional activity. Their transcriptional activity was also related to the carbon chain length and the terminal functional group. Molecular docking analysis showed the PFASs fitted into the ligand binding pocket of PPARβ/δ with a binding geometry similar to a fatty acid.			●							-		D	B
1373	MOA（肝毒性）	Long, Manhai; Ghisari, Mandana; Bonefeld-Jø rgensen, Eva Cecilie	Effects of perfluoroalkyl acids on the function of the thyroid hormone and the aryl hydrocarbon receptor	2013	Environ Sci Pollut Res Int. 2013 Nov;20(11):8045-56. doi: 10.1007/s11356-013-1628-7. Epub 2013 Mar 29.	Perfluoroalkyl acids (PFAAs) are perfluorinated compounds that widely exist in the environment and can elicit adverse effects including endocrine disruption in humans and animals. This study investigated the effect of seven PFAAs on the thyroid hormone (TH) system assessing the proliferation of the 3,3',5-triiodo-L-thryonine (T3)-dependent rat pituitary GH3 cells using the T-screen assay and the effect on the aryl hydrocarbon receptor (AhR) transactivation in the AhR-luciferase reporter gene bioassay. A dose-dependent impact on GH3 cells was observed in the range 1×10(-9)-1×10(-4) M: seven PFAAs (perfluorooctane sulfonate (PFOS), perfluorohexane sulfonate (PFHxS), perfluorooctanoic acid, perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnA), and perfluorododecanoic acid (PFDoA)) inhibited the GH3 cell growth, and four PFAAs (PFOS, PFHxS, PFNA, and PFUnA) antagonized the T3-induced GH3 cell proliferation. At the highest test concentration, PFHxS showed a further increase of the T3-induced GH3 growth. Among the seven tested PFAAs, only PFDoA and PFDA elicited an activating effect on the AhR. In conclusion, PFAAs possess in vitro endocrine-disrupting potential by interfering with TH and AhR functions, which need to be taken into consideration when assessing the impact on human health.			●							-		B	B
1374	MOA（肝毒性）	Ma, X; Stoffregen, D A; Wheelock, G D; Rininger, J A; Babish, J G	Discordant hepatic expression of the cell division control enzyme p34cdc2 kinase, proliferating cell nuclear antigen, p53 tumor suppressor protein, and p21Waf1 cyclin-dependent kinase inhibitory protein after WY14,643 ([4-chloro-6-(2,3-xylidino)-2-pyrimidinylthio]acetic acid) dosing to rats	1997	Mol Pharmacol. 1997 Jan;51(1):69-78. doi: 10.1124/mol.51.1.69.	The hepatocarcinogen and peroxisome proliferator WY14,643 ([4-chloro-6-(2,3-xylidino)-2-pyrimidinylthio]acetic acid) was examined for its ability to induce changes in the intracellular protein expression of hepatic p34cdc2 kinase (CDK1), proliferating cell nuclear antigen (PCNA), p53 tumor suppressor protein, and p21Waf1 CDK inhibiting protein. Young adult male rats were administered 45 mg-kg/day WY14,643 intraperitoneally for 1, 2, 3, 4, or 5 days or fed diets containing 0% or 0.08% WY14,643 for 1, 2, 3, or 4 weeks. WY14,643 dosing increased concentrations of hepatic proteins of 34- and 37-kDa molecular mass, which were identified through immunoprecipitation as CDK1 and PCNA, respectively. Gel filtration of the hepatic S9 fractions determined by enzyme-linked immunosorbent assay confirmed the increased expression of CDK1 and PCNA immunoreactivity in livers from WY14,643-treated rats. Also, gel filtration revealed that the native CDK1 and PCNA in hepatic S9 from WY14,643-treated rats chromatographed as a major peak with an apparent molecular mass of 70 and 76 kDa, respectively. Immunoblotting of the 70-kDa fraction with anti-CDK1 revealed a single band of molecular mass of 34 kDa. Thus, the CDK1 in the major immunoreactive peak of WY14,643-treated rat liver S9 seems to exist as a heterodimer or homodimer. Immunohistochemistry of formalin-fixed liver demonstrated a cytosolic localization of immunoreactive CDK1 and nuclear localization of immunoreactive PCNA in proliferating cells of WY14,643-treated rat livers. WY14,643 increased hepatic CDK1 content by 1.9-6.3-fold through postdosing days 1-5. Hepatic PCNA content was increased 1.9-5-fold over the same period. In the 4-week feeding study, CDK1 and PCNA expression were increased at all weekly time points by an average of 15-50-fold, respectively. Furthermore, the dietary administration of 0.08% WY14,643 resulted in sustained, overexpression of hepatic p53 tumor suppressor protein from week 1 through week 4 and of p21Waf1 CDK inhibitory protein from week 3 to week 4.			●							-		C	C
1375	in vitro（PPAR）	Ma, Yuzhong; Sachdeva, Karuna; Liu, Jirong; Song, Xiulong; Li, Yuxin; Yang, Dongfang; Deng, Ruitang; Chichester, Clinton O; Yan, Bingfang	Clofibrate and perfluorodecanoate both upregulate the expression of the pregnane X receptor but oppositely affect its ligand dependent induction on cytochrome P450 3A23	2005	Biochem Pharmacol. 2005 May 1;69(9):1363-71. doi: 10.1016/j.bcp.2005.02.011.	The pregnane X receptor (PXR) interacts with a vast array of structurally dissimilar chemicals and confers induction of several major types of drug metabolizing enzymes such as cytochrome P450s (CYP). We previously reported that the expression of PXR was markedly increased in rats treated with clofibrate and perfluorodecanoic acid (PFDA). The present study was undertaken to test the hypothesis that induced expression of PXR increases PXR ligand-dependent induction on CYP3A23. Rat hepatocytes were treated with clofibrate or PFDA individually, or along with PXR ligand pregnenolone 16alpha-carbonitrile (PCN), and the levels of PXR and CYP3A23 were determined by Western blots. Both clofibrate and PFDA markedly increased the expression of PXR with PFDA being more potent, and the induction was abolished by actinomycin D, an inhibitor for mRNA synthesis. As expected, PCN alone markedly induced the expression of CYP3A23. Interestingly, co-treatment with clofibrate enhanced the induction, whereas co-treatment with PFDA suppressed it. Clofibrate and PFDA represent multi-classes of chemicals called peroxisome proliferators including many therapeutic agents and industrial pollutants. The opposing effects of clofibrate and PFDA on the PCN-induced expression of CYP3A23 suggest that peroxisome proliferators likely increase the expression of PXR but differentially alter its ligand-dependent induction. The interaction between PXR inducer and ligand provides a novel mechanism on how functionally and structurally distinct chemicals cooperatively regulate the expression of xenobiotic-metabolizing enzymes and transporters.			●							-		C	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献クラン①抽出	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1376	MOA（肝毒性）	Naile, Jonathan E; Wiseman, Steve; Bachtold, Kali; Jones, Paul D; Giesy, John P	Transcriptional effects of perfluorinated compounds in rat hepatoma cells	2012	Chemosphere. 2012 Jan;86(3):270-7. doi: 10.1016/j.chemosphere.2011.09.044. Epub 2011 Nov 8.	Perfluorooctanesulfonate (PFOS) is the terminal degradation product of many commercially used perfluorinated compounds, and most of the toxicity testing to date has focused on its potential biological effects. While PFOS has been extensively studied, other PFCs including replacement chemicals such as perfluorobutanesulfonate (PFBS) and perfluorobutyric acid (PFBA), have not been well characterized. Despite the relative lack of data available on these other PFCs it has been assumed that they will cause similar or lesser effects than PFOS. This study compared the effects of 10 PFCs routinely found in the environment on mRNA abundance of 7 genes related to processes known to be affected by PFOS, such as fatty acid and cholesterol synthesis, and thyroid development. Rat H4IIE hepatoma cells were exposed and changes in mRNA abundance were quantified by real-time PCR. Significant changes in mRNA abundance were observed. The effects caused by the shorter chain replacement chemicals differed significantly from those caused by PFOS or PFOA. Furthermore, not all of the PFCs caused the same effects, and changes could not simply be attributed to chain-length or functional group. These differences could mean that these replacement chemicals do not act through the same mechanisms as the more studied PFOS and PFOA.			●							-		B	B
1377	MOA（肝毒性）	Nakagawa, Tomohiko; Ramdhan, Doni Hikmat; Tanaka, Naoki; Naito, Hisao; Tamada, Hazuki; Ito, Yuki; Li, Yufei; Hayashi, Yumi; Yamagishi, Nozomi; Yanagiba, Yukie; Aoyama, Toshifumi; Gonzalez, Frank J; Nakajima, Tamie	Modulation of ammonium perfluorooctanoate-induced hepatic damage by genetically different PPARa in mice	2012	Arch Toxicol. 2012 Jan;86(1):63-74. doi: 10.1007/s00204-011-0704-3. Epub 2011 Apr 17.	Perfluorooctanoic acid is a ligand for peroxisome proliferator-activated receptor (PPARα). Ammonium perfluorooctanoate (APFO) at 0.1 and 0.3 mg/kg doses activated mouse PPARα, but not human PPARα. This study aimed to clarify whether milligram-order APFO can activate human PPARα, and the receptor is involved in APFO-induced chronic hepatic damage. Male Sv/129 wild-type (mPPARα), Pparα-null, and humanized PPARα (hPPARα) mice (8 weeks old) were divided into three groups. The first was treated with water and the other two with 1.0 and 5.0 mg/kg APFO for 6 weeks, orally, respectively. Both doses activated mouse and human PPARα to a similar or lower degree in the latter. APFO dose dependently increased hepatic triglyceride levels in Pparα-null and hPPARα mice, but conversely decreased those in mPPARα ones. APFO-induced hepatic damage differed markedly among the three genotyped groups: single-cell necrosis was observed in all genotyped mice; inflammatory cells and macrovesicular steatosis only in Pparα-null mice; and microvesicular steatosis and hydropic degenerations in hPPARα and Pparα-null mice. The molecular mechanism underlying these differences may be attributable to those of gene expressions involved in lipid homeostasis (PPARα, β- and ω-oxidation enzymes, and diacylglycerol acyltransferases) and uncoupling protein 2. Thus, milligram-order APFO activated both mouse and human PPARα in a different manner, which may reflect histopathologically different types of hepatic damage.			●	●		●				-		B	C
1378	MOA（肝毒性）	Parzefall, W; Berger, W; Kainzbauer, E; Teufelhofer, O; Schulte-Hermann, R; Thurman, R G	Peroxisome proliferators do not increase DNA synthesis in purified rat hepatocytes	2001	Carcinogenesis. 2001 Mar;22(3):519-23. doi: 10.1093/carcin/22.3.519.	There have been numerous reports that chemicals which induce peroxisomes in rodent liver increase DNA synthesis in isolated hepatic parenchymal cells, but not as well in vitro as in vivo. It is also known that tumour necrosis factor alpha (TNFalpha) is mitogenic in isolated hepatocytes. Since Kupffer cells are a major source of TNFalpha in the liver and have recently been shown to be activated by peroxisome proliferators, the possibility exists that the effect of peroxisome proliferators on DNA synthesis in parenchymal cells is via Kupffer cell contamination of isolated hepatocyte preparations. The purpose of this study was to evaluate this hypothesis by studying the effect of model peroxisome proliferators on purified hepatocyte preparations. Hepatocytes were prepared from rat liver by standard calcium-free and collagenase perfusion. Subsequently, cells were centrifuged through Percoll to remove contaminating non-parenchymal cells. Cells were at least 99.9% pure as assessed by cell counting using specific markers for hepatocytes (resorufin O-glucoside) and Kupffer cells (FITC-labelled latex beads). Hepatocytes were cultured in Williams medium + 10% fetal bovine serum for 24 h followed by culture for 48 h in Williams medium plus or minus drug or mitogen additions. Under these conditions epidermal growth factor stimulated DNA synthesis assessed by incorporation of [3H]thymidine approximately 5-fold over control levels. The peroxisome proliferators WY,14-643 and nafenopin, however, had no effect on DNA synthesis, although they did increase acyl-CoA oxidase as expected. In contrast, TNFalpha increased cell proliferation nearly 10-fold in purified hepatocytes, an effect nearly doubled by WY-14,643. Further, when conditioned medium from purified Kupffer cells incubated with WY-14,643 was added to pure hepatocytes, DNA synthesis was increased over 2-fold in a time-dependent manner. Collectively, these data support the hypothesis that peroxisome proliferators do not influence DNA synthesis in isolated hepatocytes per se. Rather, they stimulate cytokine production by Kupffer cells which in turn increases DNA synthesis in parenchymal cells. An increase in mitogenic cytokine production by Kupffer cells is necessary for stimulation of DNA synthesis in purified rat parenchymal cells.			●							-		C	C
1379	MOA（肝毒性）	Pugh, G Jr; Isenberg, J S; Kamendulis, L M; Ackley, D C; Clare, L J; Brown, R; Lington, A W; Smith, J H; Klaunig, J E	Effects of di-isononyl phthalate, di-2-ethylhexyl phthalate, and clofibrate in cynomolgus monkeys	2000	Toxicol Sci. 2000 Jul;56(1):181-8. doi: 10.1093/toxsci/56.1.181.	The effects of the peroxisome proliferators di-isononyl phthalate (DINP) and di-2-ethylhexyl phthalate (DEHP) were evaluated in young adult male cynomolgus monkeys after 14 days of treatment, with emphasis on detecting hepatic and other effects seen in rats and mice after treatment with high doses of phthalates. Groups of 4 monkeys received DINP (500 mg/kg/day), DEHP (500 mg/kg/day), or vehicle (0.5% methyl cellulose, 10 ml/kg) by intragastric intubation for 14 consecutive days. Clofibrate (250 mg/kg/day), a hypolipidemic drug used for cholesterol reduction in human patients was used as a reference substance. None of the test substances had any effect on body weight or liver weights. Histopathological examination of tissues from these animals revealed no distinctive treatment-related effects in the liver, kidney, or testes. There were also no changes in any of the hepatic markers for peroxisomal proliferation, including peroxisomal beta-oxidation (PBOX) or replicative DNA synthesis. Additionally, in situ dye transfer studies using fresh liver slices revealed that DINP, DEHP, and clofibrate had no effect on gap junctional intercellular communication (GJIC). None of the test substances produced any toxicologically important changes in urinalysis, hematology, or clinical chemistry; however, clofibrate produced some emesis, small increases in serum triglyceride, decreased calcium, and decreased weights of testes/epididymides and thyroid/parathyroid. The toxicological significance of these small changes is questionable. The absence of observable hepatic effects in monkeys at doses that produce hepatic effects in rodents suggests that DINP, DEHP, and clofibrate would also not elicit in primates other effects such as liver cancer. These data, along with results from in vitro hepatocyte studies, indicate that rodents are not good animal models for predicting the hepatic effects of phthalates in primates, including humans.			●							-		C	C
1380	MOA（肝毒性）	Rand, Amy A; Rooney, John P; Butt, Craig M; Meyer, Joel N; Mabury, Scott A	Cellular toxicity associated with exposure to perfluorinated carboxylates (PFCAs) and their metabolic precursors	2014	Chem Res Toxicol. 2014 Jan 21;27(1):42-50. doi: 10.1021/tx400317p. Epub 2013 Dec 17.	The biotransformation of fluorotelomer based compounds yields saturated and unsaturated fluorotelomer aldehydes (FTALs and FTUALs, respectively) and carboxylic acids (FTCAs and FTUCAs, respectively) as intermediate metabolites that subsequently transform to perfluorinated carboxylic acids (PFCAs). Previous studies have demonstrated that the FTCAs and FTUCAs are 1 to 5 orders of magnitude more toxic than PFCAs after exposure to aquatic organisms. Additionally, FTUALs have demonstrated reactivity with proteins, which may be associated with toxicity through the inhibition of protein function. The purpose of this study was to carry out a comprehensive assessment of the relative toxicity between PFCAs and their intermediate precursor metabolites: the FTALs, FTUALs, FTCAs, and FTUCAs. Analytes were separately incubated with human liver epithelial (THLE-2) cells to assess how varying the functional group and the fluorinated chain length affects cell viability. For each analyte, dose-response EC50 values were calculated. The EC50 values for FTUCAs and FTCAs were similar, with values ranging from 22 ± 9 and 24 ± 9 μM for the 10:2 congeners to 1004 ± 20 and 1004 ± 24 μM for the 4:2 congeners, respectively. The EC50 values for the PFCAs ranged from 65 ± 41 (PFDA) to 1361 ± 146 (PFBA) μM. The range of toxicity between PFCAs and their acid precursors were similar. However, the comparative toxicity between the 6:2 and 8:2 congeners and their corresponding PFCA had toxicity thresholds that varied depending on the functional headgroup, where FTUALs ≥ FTALs > FTUCAs ≥ FTCAs > PFCAs. For all PFCAs and acid precursors, toxicity depended on the length of the fluorinated chain, where the longer chain lengths yielded greater bioaccumulation and enhanced toxicity, results which agreed with those previously reported. By contrast, FTALs and FTUALs were the most toxic of all the analytes examined, where toxicity was enhanced at shorter chain lengths, with EC50 values of 7 ± 1 μM (6:2 FTUAL) and 8.6 ± 0.8 μM (6:2 FTAL). DNA adducts were not detectable for the aldehyde precursors, using a quantitative long-range PCR method. Our data provide the first evidence that aldehyde intermediates have demonstrated toxicity in cellular systems that is more significant than PFCAs and their corresponding acid intermediates.			●							-		D	B
1381	MOA（肝毒性）	Rolfe, M; James, N H; Roberts, R A	Tumour necrosis factor alpha (TNF-alpha) suppresses apoptosis and induces DNA synthesis in rodent hepatocytes: a mediator of the hepatocarcinogenicity of peroxisome proliferators	1997	Carcinogenesis. 1997 Nov;18(11):2277-80. doi: 10.1093/carcin/18.11.2277.	Peroxisome proliferators (PPs) are a class of non-genotoxic rodent hepatocarcinogens that cause increased hepatocyte DNA synthesis, peroxisome proliferation and liver enlargement. We have demonstrated previously that PPs suppress both spontaneous rat hepatocyte apoptosis and that induced by the physiological negative regulator of liver growth, transforming growth factor beta (TGF beta1). Evidence suggests that the suppression of apoptosis by PPs is mediated via activation of the peroxisome proliferator activated receptor-alpha (PPAR alpha), a member of the nuclear hormone receptor superfamily. Here, we investigate the effects of tumour necrosis factor alpha (TNF alpha) on cultured rat or mouse hepatocytes to determine whether TNF alpha influences hepatocyte growth in a manner analogous to that seen with PPs. Rat recombinant TNF alpha was found to stimulate DNA synthesis and suppress apoptosis in isolated rat hepatocyte monolayers (P < or = 0.01). These effects were seen in the range of 500-5000 U/ml with a maximum effect at 5000 U/ml. Similarly, mouse recombinant TNF alpha was able to stimulate DNA synthesis in mouse hepatocyte monolayers (P <or = 0.01) with a maximal effect at 1000 U/ml. Suppression of mouse hepatocyte apoptosis by TNF alpha was not detected, possibly because of the low levels of apoptosis under control conditions. However, when the levels of mouse hepatocyte apoptosis were augmented using TGF beta1, TNF alpha caused a significant suppression (P < or = 0.01). The neutralization of TNF alpha using anti-TNF alpha antibodies abrogated significantly (P < or = 0.01) the suppression of apoptosis by the PP, nafenopin. These data that suggest TNF alpha may mediate, at least in part, the growth perturbation, liver enlargement and hepatocarcinogenesis seen in response to the PP class of non-genotoxic hepatocarcinogens.			●							-		C	C
1382	MOA（肝毒性）	Rose, M L; Rusyn, I; Bojes, H K; Belyea, J; Cattley, R C; Thurman, R G	Role of Kupffer cells and oxidants in signaling peroxisome proliferator-induced hepatocyte proliferation	2000	Mutat Res. 2000 Mar 17;448(2):179-92. doi: 10.1016/s0027-5107(99)00235-3.	No abstract available			●							-		D	D

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1383	MOA（肝毒性）	Rosen, Mitchell B; Lee, Janice S; Ren, Hongzu; Vallanat, Beena; Liu, Jie; Waalkes, Michael P; Abbott, Barbara D; Lau, Christopher; Corton, J Christopher	Toxicogenomic dissection of the perfluorooctanoic acid transcript profile in mouse liver: evidence for the involvement of nuclear receptors PPAR alpha and CAR	2008	Toxicol Sci. 2008 May;103(1):46-56. doi: 10.1093/toxsci/kfn025. Epub 2008 Feb 14.	A number of perfluorinated alkyl acids including perfluorooctanoic acid (PFOA) elicit effects similar to peroxisome proliferator chemicals (PPC) in mouse and rat liver. There is strong evidence that PPC cause many of their effects linked to liver cancer through the nuclear receptor peroxisome proliferator-activated receptor alpha (PPAR alpha). To determine the role of PPAR alpha in mediating PFOA transcriptional events, we compared the transcript profiles of the livers of wild-type or PPAR alpha-null mice exposed to PFOA or the PPAR alpha agonist WY-14,643 (WY). After 7 days of exposure, 85% or 99.7% of the genes altered by PFOA or WY exposure, respectively were dependent on PPAR alpha. The PPAR alpha-independent genes regulated by PFOA included those involved in lipid homeostasis and xenobiotic metabolism. Many of the lipid homeostasis genes including acyl-CoA oxidase (Acox1) were also regulated by WY in a PPAR alpha-dependent manner. The increased expression of these genes in PPAR alpha-null mice may be partly due to increases in PPAR gamma expression upon PFOA exposure. Many of the identified xenobiotic metabolism genes are known to be under control of the nuclear receptor CAR (constitutive activated/androstane receptor) and the transcription factor Nrf2 (nuclear factor erythroid 2-related factor 2). There was excellent correlation between the transcript profile of PPAR alpha-independent PFOA genes and those of activators of CAR including phenobarbital and 1,4-bis[2-(3,5-dichloropyridyloxy)] benzene (TCPOBOP) but not those regulated by the Nrf2 activator, dithiol-3-thione. These results indicate that PFOA alters most genes in wild-type mouse liver through PPAR alpha, but that a subset of genes are regulated by CAR and possibly PPAR gamma in the PPAR alpha-null mouse.			●	●						-		B	B
1384	MOA（肝毒性）	Shah, Yatrik M; Morimura, Keiichirou; Yang, Qian; Tanabe, Tomotaka; Takagi, Mitsuhiro; Gonzalez, Frank J	Peroxisome proliferator-activated receptor alpha regulates a microRNA-mediated signaling cascade responsible for hepatocellular proliferation	2007	Mol Cell Biol. 2007 Jun;27(12):4238-47. doi: 10.1128/MCB.00317-07. Epub 2007 Apr 16.	Activation of peroxisome proliferator-activated receptor alpha (PPARalpha) leads to hepatocellular proliferation and liver carcinomas. The early events mediating these effects are unknown. A novel mechanism by which PPARalpha regulates gene expression and hepatocellular proliferation was uncovered. MicroRNA (miRNA) expression profiling demonstrated that activated PPARalpha was a major regulator of hepatic miRNA expression. Of particular interest, let-7C, an miRNA important in cell growth, was inhibited following 4-h treatment and 2-week and 11-month sustained treatment with the potent PPARalpha agonist Wy-14,643 in wild-type mice. let-7C was shown to target c-myc via direct interaction with the 3' untranslated region of c-myc. The PPARalpha-mediated induction of c-myc via let-7C subsequently increased expression of the oncogenic mir-17-92 cluster; these events did not occur in Pparalpha-null mice. Overexpression of let-7C decreased c-myc and mir-17 and suppressed the growth of Hepa-1 cells. Furthermore, using the human PPARalpha-expressing mouse model, which is responsive to Wy-14,643 effects on beta-oxidation and serum triglycerides but resistant to hepatocellular proliferation and tumorigenesis, we demonstrated a critical role for let-7C in liver oncogenesis. Wy-14,643 treatment did not inhibit let-7C or induce c-myc and mir-17 expression. These observations reveal a let-7C signaling cascade critical for PPARalpha agonist-induced liver proliferation and tumorigenesis.				●						-		C	C
1385	MOA（肝毒性）	Shaw, David; Lee, Rebecca; Roberts, Ruth A	Species differences in response to the phthalate plasticizer monoisononylphthalate (MINP) in vitro: a comparison of rat and human hepatocytes	2002	Arch Toxicol. 2002 Jun;76(5-6):344-50. doi: 10.1007/s00204-002-0342-x. Epub 2002 Apr 19.	Diisononylphthalate (DINP) is one of the group of dialkyl phthalate esters used widely to impart flexibility to polyvinyl chloride (PVC) products. However, DINP and other phthalates are rodent peroxisome proliferators (PPs), a class of compounds that cause rodent hepatic peroxisome proliferation, induction of DNA synthesis and suppression of apoptosis leading to liver tumours. Despite these adverse effects in rodent liver, humans appear to be nonresponsive to the adverse effects of PPs. Here, we have examined species differences in the response of rat and human hepatocytes to MINP, a principle metabolite of DINP and the proximal peroxisome proliferator. In rat hepatocytes in vitro, MINP caused a concentration-dependent induction of peroxisomal beta-oxidation. Similarly, MINP caused a concentration-dependent suppression of apoptosis and induction of DNA synthesis. In contrast to the pleiotropic response noted in rat hepatocytes, MINP did not cause induction of beta-oxidation, stimulation of DNA synthesis or suppression of apoptosis in human hepatocytes. These data provide evidence for species differences in the hepatic response to the phthalate ester DINP, confirming that human hepatocytes are refractory to the adverse effects noted in rodents.				●						-		C	C
1386	MOA（肝毒性）	Tateno, Chise; Yamamoto, Toshinobu; Utoh, Rie; Yamasaki, Chihiro; Ishida, Yuji; Myoken, Yuka; Oofusa, Ken; Okada, Miyoko; Tsutsui, Naohisa; Yoshizato, Katsutoshi	Chimeric mice with hepatocyte-humanized liver as an appropriate model to study human peroxisome proliferator-activated receptor-a	2015	Toxicol Pathol. 2015 Feb;43(2):233-48. doi: 10.1177/0192623314544378. Epub 2014 Aug 8.	Peroxisome proliferator (PP)-activated receptor-α (PPARα) agonists exhibit species-specific effects on livers of the rodent and human (h), which has been considered to reside in the difference of PPARα gene structures. However, the contribution of h-hepatocytes (heps) to the species-specificity remains to be clarified. In this study, the effects of fenofibrate were investigated using a hepatocyte-humanized chimeric mouse (m) model whose livers were replaced with h-heps at >70%. Fenofibrate induced hepatocellular hypertrophy, cell proliferation, and peroxisome proliferation in livers of severe combined immunodeficiency (SCID) mice, but not in the h-hep of chimeric mouse livers. Fenofibrate increased the expression of the enzymes of β- and ω-hydroxylation and deoxygenation of lipids at both gene and protein levels in SCID mouse livers, but not in the h-heps of chimeric mouse livers, supporting the studies with h-PPARα-transgenic mice, a hitherto reliable model for studying the regulation of h-PPARα in the h-liver in most respects, except the induction of the peroxisome proliferation. This study indicates the importance of not only h-PPARα gene but also h-heps themselves to correctly predict effects of fibrates on h-livers, and, therefore, suggests that the chimeric mouse is a currently available, consistent, and reliable model to obtain pharmaceutical data concerning the effects of fibrates on h-livers.				●						-		C	C
1387	MOA（肝毒性）	Thomas, Maria; Bayha, Christine; Klein, Kathrin; Müller, Simon; Weiss, Thomas S; Schwab, Matthias; Zanger, Ulrich M	The truncated splice variant of € peroxisome proliferator-activated receptor alpha, PPARa-tr, autonomously regulates proliferative and pro inflammatory genes	2015	BMC Cancer. 2015 Jun 30;15:488. doi: 10.1186/s12885-015-1500-x.	BACKGROUND: The peroxisome proliferator-activated receptor alpha (PPARα) controls lipid/energy homeostasis and inflammatory responses. The truncated splice variant PPARα-tr was suggested to exert a dominant negative function despite being unable to bind consensus PPARα DNA response elements. METHODS: The distribution and variability factor of each PPARα variant were assessed in the well-characterized cohort of human liver samples (N = 150) on the mRNA and protein levels. Specific siRNA-mediated downregulation of each transcript as well as specific overexpression with subsequent qRT-PCR analysis of downstream genes was used for investigation of specific functional roles of PPARα-wt and PPARα-tr forms in primary human hepatocytes. RESULTS: Bioinformatic analyses of genome-wide liver expression profiling data suggested a possible role of PPARα-tr in downregulating proliferative and pro-inflammatory genes. Specific gene silencing of both forms in primary human hepatocytes showed that induction of metabolic PPARα-target genes by agonist WY14,643 was prevented by PPARα-wt knock-down but neither prevented nor augmented by PPARα-tr knock-down. WY14,643 treatment did not induce proliferative genes including MYC, CDK1, and PCNA, and knock-down of PPARα-wt had no effect, while PPARα-tr knock-down caused up to 3-fold induction of these genes. Similarly, induction of pro-inflammatory genes IL1B, PTGS2, and CCL2 by IL-6 was augmented by knock-down of PPARα-tr but not of PPARα-wt. In contrast to human proliferative genes, orthologous mouse genes were readily inducible by WY14,643 in PPARα-tr non-expressing AML12 mouse hepatocytes. Induction was augmented by overexpression of PPARα-wt and attenuated by overexpression of PPARα-tr. Pro-inflammatory genes including IL-1β, CCL2 and TNFα were induced by WY14,643 in mouse and human cells and both PPARα forms attenuated induction. As potential mechanism of PPARα-tr inhibitory action we suggest crosstalk with WNT/β-catenin pathway. Finally, treatment with WY14,643 in the presence of PPARα-tr resulted in the significant reduction of cell viability of AML12 and human ovarian cancer cell line, SKOV3. CONCLUSIONS: Our data suggest that the truncated PPARα splice variant functions as an endogenous inhibitor of proliferative and pro-inflammatory genes in human cells and that its absence in mouse may explain species-specific differences in fibrate-induced hepatocarcinogenesis.				●						-		C	C
1388	MOA（肝毒性）	Urbanek-Olejnik, Katarzyna; Liszewska, Monika; Winczura, Alicja; Kostka, Grażyna	Changes of c-Myc and DNMT1 mRNA and protein levels in the rat livers induced by dibutyl phthalate treatment	2016	Toxicol Ind Health. 2016 May;32(5):801-8. doi: 10.1177/0748233713512363. Epub 2013 Dec 5.	We investigated the relationship between dibutyl phthalate (DBP)-induced hypomethylation of the c-Myc promoter region (as evident in our early study) and the expression of c-Myc and DNMT1 genes (at messenger RNA (mRNA) and protein level) in the rat liver. Male Wistar rats received DBP in 1, 3, or 14 daily doses of 1800 mg kg(-1) body weight. Levels of DNMT1, c-Myc mRNA, and proteins were detected using real-time polymerase chain reaction and Western blot analysis, respectively. Our findings indicate that DBP caused an increase in mRNA levels of c-Myc at all time points. The results showed that protein levels of c-Myc in rat liver also increased significantly by DBP treatment, which were more pronounced at last time point (after 14 doses). Furthermore, overexpression of DNMT1gene have been found after one dose of DBP, which was confirmed at the protein level by Western blot analysis. Reduced levels of DNMT1mRNA and proteins (3 and 14 doses) were coordinated with depletion DNA synthesis (reported previously). Based on our previous results and those presented here, the following conclusion could be drawn: (1) DBP exerted biological activity through epigenetic modulation of c-Myc gene expression; (2) it seems possible that DBP-induced active demethylation of c-Myc gene through mechanism(s) linked to generation of reactive oxygen species by activated c-Myc; and (3) control of DNA replication was not directly dependent on c-Myc transcriptional activity and we attribute this finding to DNMT1gene expression which was tightly coordinated with DNA synthesis.				●						-		C	C
1389	MOA（肝毒性）	West, D A; James, N H; Cosulich, S C; Holden, P R; Brindle, R; Rolfe, M; Roberts, R A	Role for tumour necrosis factor a (TNFa) receptor 1 (TNFR1) and interleukin 1 receptor (IL1R) in the suppression of apoptosis by peroxisome proliferators	1999	Hepatology. 1999 Dec;30(6):1417-24. doi: 10.1002/hep.510300612.	Peroxisome proliferators (PPs) cause rodent liver enlargement and tumors. In vitro, PPs induce rat and mouse hepatocyte DNA synthesis and suppress apoptosis, a response mimicked by exogenous tumor necrosis factor alpha (TNFalpha). Here, we determine the role of TNF receptor 1 (TNFR1), TNF receptor 2 (TNFR2), and nuclear factor kappa beta (NFkappaB) in the response of mouse hepatocytes to the PP, nafenopin. Nafenopin (50 micromol/L) induced DNA synthesis as measured by bromodeoxyuridine (BrdU) incorporation, suppressed cell death as measured by Hoechst 33258 staining, induced peroxisomal beta-oxidation as measured by cyanide insensitive palmitoyl CoA oxidation (PCO) and caused activation of nuclear factor kappa beta (NFkappaB) as determined by electrophoretic mobility gel shift assay (EMSA). The induction of DNA synthesis and the suppression of apoptosis in response to nafenopin was abrogated completely by blocking antibodies to TNFR1 but not to TNFR2. In contrast, the induction of peroxisomal beta-oxidation by nafenopin was not blocked by the anti-TNFR1 antibody. Next, we evaluated the response of hepatocytes to interleukin-1 (IL-1), another proinflammatory cytokine. IL-1alpha (2.5 ng/mL) and, to a lesser extent, IL-1beta (5 ng/mL), shared the ability of TNFalpha to induce DNA synthesis and suppress apoptosis. In addition, anti-IL-1 receptor, type 1/p80 (IL-1R) antibodies were able to abrogate the response to nafenopin. IL-1alpha was still able to perturb hepatocyte growth in the presence of the anti-TNFR1 antibody suggesting that IL-1alpha acts independently rather than by elaborating TNFalpha. In summary, these data provide additional evidence for a role for hepatic cytokines in the perturbation of hepatocyte growth by PPs such as nafenopin.				●						-		C	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報抽出対象	文献ランク①	文献ランク②
1390	実験動物（肝毒性）	Wolf, Douglas C; Moore, Tanya; Abbott, Barbara D; Rosen, Mitchell B; Das, Kaberi P; Zehr, Robert D; Lindstrom, Andrew B; Strynar, Mark J; Lau, Christopher	Comparative hepatic effects of perfluorooctanoic acid and WY 14,643 in PPAR-alpha knockout and wild-type mice	2008	Toxicol Pathol. 2008 Jun;36(4):632-9. doi: 10.1177/0192623308318216. Epub 2008 May 8.	Perfluorooctanoic acid (PFOA) is a chemical used in the production of fluoropolymers. Its persistence in the environment and presence in humans and wildlife has raised health concerns. Liver tumor induction by PFOA is thought to be mediated in rodents by PPAR-alpha. A recent US EPA scientific advisory board questioned the contribution of PPAR-alpha in PFOA-induced liver tumors. Liver response in CD-1, SV/129 wild-type (WT), and PPAR-alpha knockout (KO) SV/129 mice was evaluated after seven daily treatments of PFOA-NH4(+) (1, 3, or 10 mg/kg, p.o.) or the prototype PPARalpha-agonist Wyeth 14,643 (WY, 50 mg/kg). Livers were examined by light and electron microscopy. Proliferation was quantified after PCNA immunostaining. PFOA treatment induced a dose-dependent increase in hepatocyte hypertrophy and labeling index (LI) similar to WY in WT mice. Ultrastructural alterations of peroxisome proliferation were similar between WY-treated and 10 mg/kg PFOA-treated WT mice. KO mice had a dose-dependent increase in hepatocyte vacuolation but increased LI only at 10 mg PFOA/kg. WY-treated KO mice were not different from KO control. These data suggest that PPAR-alpha is required for WY- and PFOA-induced cellular alterations in WT mouse liver. Hepatic enlargement observed in KO mice may be due to an accumulation of cytoplasmic vacuoles that contain PFOA.			●	●		●				MOA（肝毒性）→実験動物	1	A	B
1391	in vitro（PPAR）	Wolf, Cynthia J; Schmid, Judith E; Lau, Christopher; Abbott, Barbara D	Activation of mouse and human peroxisome proliferator-activated receptor-alpha (PPARa) by perfluoroalkyl acids (PFAAs): further investigation of C4-C12 compounds	2012	Reprod Toxicol. 2012 Jul;33(4):546-551. doi: 10.1016/j.reprotox.2011.09.009. Epub 2011 Nov 15.	Perfluorinated alkyl acids (PFAAs) are manufactured surfactants found globally in the environment and in tissues of humans and wildlife. Several PFAAs adversely affect rodents and activation of PPARα is thought to be their mode of action. Our previous study demonstrated that some PFAAs activate mouse and human PPARα in transiently transfected COS-1 cells. Here, we test more PFAAs for PPARα activation in the same system. Cells were transfected with either mouse or human PPARα-luciferase reporter plasmid, exposed the next day to either vehicle, PPARα agonist (WY14643), perfluoropentanoic acid (C5), perfluoroheptanoic acid (C7), perfluorooctanoic acid (C8), perfluoroundecanoic acid (C11), or perfluorododecanoic acid (C12) at concentrations from 0.5μM to 100μM, and luminescence was measured after 24h. C8 induced the highest activity for human PPARα, followed by C7, C5, and C11. C12 had little activity. C8 induced the highest activity for mouse PPARα, followed by C11, C7, C12 and C5. The two studies together found increasing activity of PPARα with increasing chain length of the PFAA up to perfluorononanoic acid (C9) and lower activity with longer chain PFAAs with both mouse and human PPARα.			●	●						-		B	A
1392	MOA（肝毒性）	Wong, Fiona; MacLeod, Matthew; Mueller, Jochen F; Cousins, Ian T	Response to Comment on "Enhanced Elimination of Perfluorooctane Sulfonic Acid by Menstruating Women: evidence from population-based pharmacokinetic modeling	2015	Environ Sci Technol. 2015 May 5;49(9):5838-9. doi: 10.1021/acs.est.5b00981. Epub 2015 Apr 14.	No abstract available			●	●						コメント		D	D
1393	MOA（肝毒性）	Yang, Qian; Nagano, Tomokazu; Shah, Yatrik; Cheung, Connie; Ito, Shinji; Gonzalez, Frank J	The PPAR alpha-humanized mouse: a model to investigate species differences in liver toxicity mediated by PPAR alpha	2008	Toxicol Sci. 2008 Jan;101(1):132-9. doi: 10.1093/toxsci/kfm206. Epub 2007 Aug 9.	To determine the impact of the species difference between rodents and humans in response to peroxisome proliferators (PPs) mediated by peroxisome proliferator-activated receptor (PPAR)alpha, PPAR alpha-humanized transgenic mice were generated using a P1 phage artificial chromosome (PAC) genomic clone bred onto a ppar alpha-null mouse background, designated hPPAR alpha PAC. In hPPAR alpha PAC mice, the human PPAR alpha gene is expressed in tissues with high fatty acid catabolism and induced upon fasting, similar to mouse PPAR alpha in wild-type (Wt) mice. Upon treatment with the PP fenofibrate, hPPAR alpha PAC mice exhibited responses similar to Wt mice, including peroxisome proliferation, lowering of serum triglycerides, and induction of PPAR alpha target genes encoding enzymes involved in fatty acid metabolism in liver, kidney, and heart, suggesting that human PPAR alpha (hPPAR alpha) functions in the same manner as mouse PPAR alpha in regulating fatty acid metabolism and lowering serum triglycerides. However, in contrast to Wt mice, treatment of hPPAR alpha PAC mice with fenofibrate did not cause significant hepatomegaly and hepatocyte proliferation, thus indicating that the mechanisms by which PPAR alpha affects lipid metabolism are distinct from the hepatocyte proliferation response, the latter of which is only induced by mouse PPAR alpha. In addition, a differential regulation of several genes, including the oncogenic let-7C miRNA by PPs, was observed between Wt and hPPAR alpha PAC mice that may contribute to the inherent difference between mouse and human PPAR alpha in activation of hepatocellular proliferation. The hPPAR alpha PAC mouse model provides an in vivo platform to investigate the species difference mediated by PPAR alpha and an ideal model for human risk assessment PPs exposure.			●							-		C	C
1394	MOA（PPAR）	Abbott, B. D.; Wood, C. R.; Watkins, A. M.; Das, K. P.; Lau, C. S.	Peroxisome proliferator-activated receptors alpha, beta, and gamma mRNA and protein expression in human fetal tissues	2012	PPAR Res. 10.1155/2010/690907. doi: 10.1155/2010/690907. Epub 2010 Jul 26.	Peroxisome proliferator-activated receptors (PPARs) regulate lipid and glucose homeostasis, are targets of pharmaceuticals, and are also activated by environmental contaminants. Almost nothing is known about expression of PPARs during human fetal development. This study examines expression of PPARalpha, beta, and gamma mRNA and protein in human fetal tissues. With increasing fetal age, mRNA expression of PPARalpha and beta increased in liver, but PPARbeta decreased in heart and intestine, and PPARgamma decreased in adrenal. Adult and fetal mean expression of PPARalpha, beta, and gamma mRNA did not differ in intestine, but expression was lower in fetal stomach and heart. PPARalpha and beta mRNA in kidney and spleen, and PPARgamma mRNA in lung and adrenal were lower in fetal versus adult. PPARgamma in liver and PPARbeta mRNA in thymus were higher in fetal versus adult. PPARalpha protein increased with fetal age in intestine and decreased in lung, kidney, and adrenal. PPARbeta protein in adrenal and PPARgamma in kidney decreased with fetal age. This study provides new information on expression of PPAR subtypes during human development and will be important in evaluating the potential for the developing human to respond to PPAR environmental or pharmaceutical agonists.				●						-		C	C
1395	実験動物（肝毒性）	Abdellatif, A G; Préat, V; Taper, H S; Roberfroid, M	The modulation of rat liver carcinogenesis by perfluorooctanoic acid, a peroxisome proliferator	1991	Toxicol Appl Pharmacol. 1991 Dec;111(3):530-7. doi: 10.1016/0041-008x(91)90257-f.	Perfluorooctanoic acid (PFOA) is a peroxisome proliferator. The aim of this study was to test for its ability to act as a positive modulator of hepatocarcinogenesis, in the so-called biphasic (initiation by diethylnitrosamine 200 mg/kg ip followed by treatment with the suspected modulators) and triphasic (initiation by the same dose of diethylnitrosamine followed by a selection procedure for 2 weeks consisting of giving 2-acetylaminofluorene and in the middle of this treatment a single dose of CCl4 followed by treatment with the suspected modulators) protocols of liver carcinogenesis. In both protocols treatment with PFOA increased the incidence of malignant hepatocellular carcinoma (HCC). As compared to phenobarbital, the modulating effect of PFOA is more pronounced in a biphasic than in the triphasic protocol. In parallel with positive modulation of HCC, PFOA also selectively induced the peroxisomal acyl-CoA oxidase activity and, to a lesser extent, catalase activity.				●						-		B	B
1396	実験動物（肝毒性）	Ahmed, D. Y.; Abd Ellah, M. R.	Effect of exposure to perfluorooctanoic acid on hepatic antioxidants in mice	2012	Comp Clin Pathol. 21(6):1643-1645. doi: 10.1007/s00580-011-1341-1	The present study was undertaken to evaluate hepatic antioxidants status in female mice after exposure to perfluorooctanoic acid (PFOA). A total number of 20 female mice were subjected to the study; out of them, 15 mice were treated with PFOA. PFOA solutions were prepared at 0.1, 0.5, and 1 mg/ml of deionized water and administered to the mice by gavage once daily for 3 weeks at a volume of 10 ml/kg. Controls (five mice) received an equivalent volume of deionized water. The results revealed significant increase in liver weight at dose of 5 ($p < 0.01$) and 10 mg/kg body weight (b.w., $p < 0.01$). Both hepatic total glutathione level and hepatic catalase activity were significantly increased ($p < 0.01$) at dose of 5 mg/kg b.w. On the other hand, hepatic glutathione reductase activity was significantly increased at dose of 10 mg/kg b.w. In this model system, PFOA administration was effective in inducing oxidative stress particularly reflected in the liver.				●						-		B	B
1397	実験動物（肝毒性）	Cattley RC, DeLuca J, Elcombe C, Fenner-Crisp P, Lake BG, Marsman DS, Pastoor TA, Popp JA, Robinson DE, Schwetz B, Tugwood J, Wahli W.	Do peroxisome proliferating compounds pose a hepatocarcinogenic hazard to humans?	1998	Regul Toxicol Pharmacol. 1998 Feb;27(1 Pt 2):47-60. doi: 10.1006/rtph.1997.1163	The purpose of the workshop "Do Peroxisome Proliferating Compounds Pose a Hepatocarcinogenic Hazard to Humans?" was to provide a review of the current state of the science on the relationship between peroxisome proliferation and hepatocarcinogenesis. There has been much debate regarding the mechanism by which peroxisome proliferators may induce liver tumors in rats and mice and whether these events occur in humans. A primary goal of the workshop was to determine where consensus might be reached regarding the interpretation of these data relative to the assessment of potential human risks. A core set of biochemical and cellular events has been identified in the rodent strains that are susceptible to the hepatocarcinogenic effects of peroxisome proliferators, including peroxisome proliferation, increases in fatty acyl-CoA oxidase levels, microsomal fatty acid oxidation, excess production of hydrogen peroxide, increases in rates of cell proliferation, and expression and activation of the alpha subtype of the peroxisome proliferator-activated receptor (PPAR-alpha). Such effects have not been identified clinically in liver biopsies from humans exposed to peroxisome proliferators or in in vitro studies with human hepatocytes, although PPAR-alpha is expressed at a very low level in human liver. Consensus was reached regarding the significant intermediary roles of cell proliferation and PPAR-alpha receptor expression and activation in tumor formation. Information considered necessary for characterizing a compound as a peroxisome proliferating hepatocarcinogen include hepatomegaly, enhanced cell proliferation, and an increase in hepatic acyl-CoA oxidase and/or palmitoyl-CoA oxidation levels. Given the lack of genotoxic potential of most peroxisome proliferating agents, and since humans appear likely to be refractive or insensitive to the tumorigenic response, risk assessments based on tumor data may not be appropriate. However, nontumor data on intermediate endpoints would provide appropriate toxicological endpoints to determine a point of departure such as the LED10 or NOAEL which would be the basis for a margin-of-exposure (MOE) risk assessment approach. Pertinent factors to be considered in the MOE evaluation would include the slope of the dose-response curve at the point of departure, the background exposure levels, and variability in the human response.				●						-		D	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献ラン①①	文献ラン②②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1398	実験動物（肝毒性）	Elcombe, Clifford R; Elcombe, Barbara M; Foster, John R; Chang, Shu-Ching; Ehresman, David J; Noker, Patricia E; Butenhoff, John L	Evaluation of hepatic and thyroid responses in male Sprague Dawley rats for up to eighty-four days following seven days of dietary exposure to potassium perfluorooctanesulfonate	2012	Toxicology. 2012 Mar 11;293(1-3):30-40. doi: 10.1016/j.tox.2011.12.015. Epub 2012 Jan 8.	In a prior 28-day dietary study in rats with 20 and 100 ppm K⁺ PFOS, activation of PPARα and CAR/PXR were concluded to be etiological factors in K⁺ PFOS-induced hepatomegaly and hepatic tumorigenesis. The objective of this study was to evaluate persistence/resolution of K⁺ PFOS-induced, liver-related effects in male Sprague Dawley rats following a 7-day dietary exposure to K⁺ PFOS at 20 or 100 ppm. Groups of 10 rats per treatment were observed on recovery Day(s) 1, 28, 56, and 84 following treatment. Changes consistent with hepatic PPARα and CAR/PXR activation noted on recovery Day 1 included: increased liver weight; decreased plasma cholesterol, alanine aminotransferase, and triglycerides; decreased liver DNA concentration and increased hepatocellular cytosolic CYP450 concentration; increased liver activity of acyl CoA oxidase, CYP4A, CYP2B, and CYP3A; increased liver proliferative index and decreased liver apoptotic index; decreased hepatocellular glycogen-induced vacuoles; increased centrilobular hepatocellular hypertrophy. Most effects resolved to control levels during recovery. Effects on plasma cholesterol, hepatocellular cytosolic CYP450 concentrations, liver apoptotic index, CYP3A, and centrilobular hepatocellular hypertrophy persisted through the end of the recovery period. Thyroid parameters (histology, apoptosis, and proliferation) were unaffected at all time points. Mean serum PFOS concentrations on recovery Day 1 were 39 and 140 µg/mL (20 ppm and 100 ppm K⁺ PFOS, respectively), decreasing to 4 and 26 µg/mL by recovery Day 84. Thus, hepatic effects in male rats resulting from K⁺ PFOS-induced activation of PPAR and CAR/PXR resolved slowly or were still present after 84-days following a 7-day dietary treatment, consistent with the slow elimination rate of PFOS.				●	●				●	-		B	B
1399	実験動物（肝毒性）	Elcombe, Clifford R; Elcombe, Barbara M; Foster, John R; Chang, Shu-Ching; Ehresman, David J; Butenhoff, John L	Hepatocellular hypertrophy and cell proliferation in Sprague-Dawley rats from dietary exposure to potassium perfluorooctanesulfonate results from increased expression of xenosensor nuclear receptors PPARα and CAR/PXR	2012	Toxicology. 2012 Mar 11;293(1-3):16-29. doi: 10.1016/j.tox.2011.12.014. Epub 2012 Jan 8.	The present study investigated the potential role for activation of PPARα and CAR/PXR by potassium PFOS (K⁺ PFOS) with respect to the etiology of hepatic hypertrophy and hepatocellular adenoma in rats. Male Sprague-Dawley rats were fed K⁺ PFOS (20 or 100 ppm) for either 1, 7, or 28 days. Wyeth 14,643 (Wy 14,643, 50 ppm) and phenobarbital (PB, 500 ppm) were the controls for PPARα and CAR/PXR activation, respectively. Measurements included: plasma ALT, AST, cholesterol, triglycerides, and glucose; liver protein and DNA content; liver activities of palmitoyl CoA oxidase (ACOX), Cyp4A, CYP2B, and CYP3A; induction of liver CYP4A1, CYP2E1, CYP2B1/2, and CYP3A1 proteins (SDS-PAGE and Western blots); liver and thyroid microscopic histopathology, apoptotic index, and cell proliferation index. Terminal body weight was decreased by K⁺ PFOS (100 ppm) and Wy 14,643. All test-compound treatments increased liver weight. Plasma lipids were decreased by both PFOS and Wy 14,643. After treatment for 1 day, K⁺ PFOS (100 ppm), PB, and Wy 14,643 increased mean hepatic DNA concentration and total hepatic DNA, and total DNA remained elevated after treatment for 7 days and 28 days (PB and Wy 14,643 only). Hepatic P450 concentration was elevated after 7 and 28 days by K⁺ PFOS and by PB. K⁺ PFOS and Wy 14,643 increased liver activities of ACOX and CYP4A as well as increased liver CYP4A1 protein. By 28 days of treatment, K⁺ PFOS and PB increased liver activities of CYP2B and CYP3A as well as increased liver CYP2B1/2 and CYP3A1 proteins, and Wy 14,643 increased CYP2B enzyme activity to a slight extent. All test compounds increased the liver cell proliferative index and decreased the liver apoptotic index. No histological changes of the thyroid were noted; however, PB and WY increased thyroid follicular cell proliferation index (seven-day treatment only), while K⁺ PFOS did not. The thyroid follicular cell apoptotic index did not differ between groups. The hepatomegaly and hepatocellular adenoma observed after dietary exposure of Sprague-Dawley rats to K⁺ PFOS likely are due to the increased expression of xenosensor nuclear receptors PPARα and CAR/PXR. Given the markedly lower or absent response of human hepatocytes to the proliferative stimulus from activation of PPARα and CAR/PXR, the hepatocellular proliferative response from activation of these receptors by PFOS observed in rats is not expected to be of human relevance.				●	●					-		B	B
1400	実験動物（肝毒性）	Eldasher, Lobna M; Wen, Xia; Little, Michael S; Bircsak, Kristin M; Yacovino, Lindsay L; Aleksunes, Lauren M	Hepatic and renal Bcrp transporter expression in mice treated with perfluorooctanoic acid	2013	Toxicology. 2013 Apr 5;306:108-13. doi: 10.1016/j.tox.2013.02.009. Epub 2013 Feb 19.	The breast cancer resistance protein (Bcrp) is an efflux transporter that participates in the biliary and renal excretion of drugs and environmental chemicals. Recent evidence suggests that pharmacological activation of the peroxisome proliferator activated receptor alpha (PPARα) can up-regulate the hepatic expression of Bcrp. The current study investigated the regulation of hepatic and renal Bcrp mRNA and protein in mice treated with the PPARα agonist perfluorooctanoic acid (PFOA) and the ability of PFOA to alter human BCRP function in vitro. Bcrp mRNA and protein expression were quantified in the livers and kidneys of male C57BL/6 mice treated with vehicle or PFOA (1 or 3mg/kg/day oral gavage) for 7 days. PFOA treatment increased liver weights as well as the hepatic mRNA and protein expression of the PPARα target gene, cytochrome P450 4a14. Compared to vehicle-treated control mice, PFOA increased hepatic Bcrp mRNA and protein between 1.5- and 3-fold. Immunofluorescent staining confirmed enhanced canalicular Bcrp staining in liver sections from PFOA-treated mice. The kidney expression of cytochrome P450 4a14 mRNA, but not Bcrp, was increased in mice treated with PFOA. Micromolar concentrations of PFOA decreased human BCRP ATPase activity and inhibited BCRP-mediated transport in inverted membrane vesicles. Together, these studies demonstrate that PFOA induces hepatic Bcrp expression in mice and may inhibit human BCRP transporter function at concentrations that exceed levels observed in humans.				●						-		D	B
1401	実験動物（肝毒性）	Fang, Xuemei; Zou, Shanshan; Zhao, Yuanyuan; Cui, Ruina; Zhang, Wei; Hu, Jiayue; Dai, Jiayin	Kupffer cells suppress perfluorononanoic acid-induced hepatic peroxisome proliferator-activated receptor alpha expression by releasing cytokines	2012	Arch Toxicol. 2012 Oct;86(10):1515-25. doi: 10.1007/s00204-012-0877-4. Epub 2012 May 31.	Kupffer cells (KCs) have been demonstrated to play a role in the regulation of intra-hepatic lipid metabolism through the synthesis and secretion of biologically active products. The involvement of KCs in the disturbance of lipid metabolism that induced by perfluorononanoic acid (PFNA), a known agonist of the peroxisome proliferator-activated receptor alpha (PPARα), was investigated in this study. Rats were exposed to PFNA or PFNA combined with gadolinium chloride, an inhibitor of KCs, for 14 days. PFNA exposure dose-dependently increased absolute and relative liver weights, induced triglyceride accumulation, up-regulated the expression of both SERBP-1c and PPARα, and stimulated the release of TNFα and IL-1β. Inactivation of KCs markedly lowered TNFα and IL-1β level, enhanced PFNA-induced expression of PPARα and its target genes, and reduced liver triglyceride levels. In vitro, PFNA-induced expression of PPARα in primary cultured hepatocytes was suppressed by recombinant rat TNFα and IL-1β. However, inhibition of the NF-κB pathway prevented this. Transient transfection and promoter analysis further revealed that these two cytokines and NF-κB were coordinately involved in the suppression of PPARα promoter activity. Our data demonstrate that TNFα and IL-1β released from KCs following PFNA exposure can suppress the expression of PPARα via NF-κB pathway, which partially contribute to the evident accumulation of triglycerides in rat liver.				●					●	-		C	B
1402	実験動物（肝毒性）	Goecke-Flora, C M; Reo, N V	Influence of carbon chain length on the hepatic effects of perfluorinated fatty acids	1996	Chem Res Toxicol. 1996 Jun;9(4):689-95. doi: 10.1021/tx950217k.	Using nuclear magnetic resonance (NMR) spectroscopy, we investigated the importance of carbon chain length with regard to the hepatic effects associated with perfluoro-n-carboxylic acids. Male F-344 rats were administered a single intraperitoneal dose of either perfluoro-n-heptanoic acid (C7-PFA), perfluoro-n-nonanoic acid (C9-PFA), or perfluoro-n-undecanoic acid (C11-PFA). Data from previous studies involving perfluoro-n-octanoic acid (C8-PFA) and perfluoro-n-decanoic acid (C10-PFA) are included for comparison. Food consumption/body weight was monitored daily for all groups. C9- and C11-PFA treatment yields a prolonged hypophagic response while C7-PFA shows a more acute response. Fluorine-19 NMR spectra of urine and bile samples show no evidence of fluorometabolites and suggest that the distribution of perfluorocarbons into urine or bile is dependent upon carbon chain length. The aqueous solubility of C7-PFA appears to facilitate rapid urinary excretion, similar to that observed for C8-PFA. The relative hydrophobicity of C9- and C11-PFA appears to favor biliary enterohepatic recirculation, yielding a more protracted toxicity, similar to C10-PFA. Phosphorus-31 NMR studies of liver in vivo and liver extracts show that perfluorocarbons of > or = C9 carbons produce a significant increase in liver phosphocholine concentration. These data are discussed with regard to the impact of these chemicals on hepatic phospholipid metabolism. Hepatic peroxisomal fatty acyl CoA-oxidase activity (FAO) was measured to determine if C7-, C9-, and C11-PFA are peroxisome proliferators. Data indicate that the induction of peroxisomal enzyme activity by perfluorocarbons requires a chain length greater than seven carbons. In general, these results demonstrate the significance of carbon chain length in the hepatotoxic response and provide clues toward understanding the processes involved in the biological activities associated with exposure to these compounds.				●						-		C	B
1403	実験動物（肝毒性）	Hu W, Jones PD, Upham BL, Trosko JE, Lau C, Giesy JP.	Inhibition of gap junctional intercellular communication by perfluorinated compounds in rat liver and dolphin kidney epithelial cell lines in vitro and Sprague-Dawley rats in vivo	2002	Toxicol Sci. 2002 Aug;68(2):429-36. doi: 10.1093/toxsci/68.2.429.	Gap junctional intercellular communication (GJIC) is the major pathway of intercellular signal transduction, and is thus important for normal cell growth and function. Recent studies have revealed a global distribution of some perfluorinated organic compounds, especially perfluorooctane sulfonic acid (PFOS) in the environment. Because other perfluoroalkanes had been shown to inhibit GJIC, the effects of PFOS and related sulfonated fluorochemicals on GJIC were studied using a rat liver epithelial cell line (WB-F344) and a dolphin kidney epithelial cell line (CDK). In vivo effects on GJIC were studied in Sprague-Dawley rats orally exposed to PFOS for 3 days or 3 weeks. Effects on GJIC were measured using the scrape loading dye technique. PFOS, perfluorooctane sulfonamide (PFOSA), and perfluorohexane sulfonic acid (PFHA) were found to inhibit GJIC in a dose-dependent fashion, and this inhibition occurred rapidly and was reversible. Perfluorobutane sulfonic acid (PFBS) showed no significant effects on GJIC within the concentration range tested. A structure activity relationship was established among all 4 tested compounds, indicating that the inhibitory effect was determined by the length of fluorinated tail and not by the nature of the functional group. The results of the studies of the 2 cell lines and the in vivo exposure were comparable, suggesting that the inhibitory effects of the selected perfluorinated compounds on GJIC were neither species- nor tissue-specific and can occur both in vitro and in vivo.				●						-		D	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①B	文献クラン②B
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1404	実験動物（肝毒性）	Ikeda, T; Aiba, K; Fukuda, K; Tanaka, M	The induction of peroxisome proliferation in rat liver by perfluorinated fatty acids, metabolically inert derivatives of fatty acids	1985	J Biochem. 1985 Aug;98(2):475-82. doi: 10.1093/oxfordjournals.jbchem.a135302.	The induction of peroxisome proliferation in rat liver was examined after administration of perfluoro-n-decanoic acid (PFDA, C10), perfluoro-n-octanoic acid (PFOA, C8), perfluoro-n-butyric acid (PFBA, C4), 1-H,1-H-pentadecafluoro-n-octanol (PFOL, C8) perfluorododecane (PFD, C12), and perfluorooctane (PFO, C8). The peroxisome proliferation in the liver was detected by the following methods; 1) measurement of liver weight, 2) assay of hepatic catalase activity, 3) analysis of 600 X g supernatant of liver homogenates by SDS-polyacrylamide gel electrophoresis to observe the induction of the bifunctional enoyl-CoA hydratase in peroxisomes (80K-protein) and 4) observation by electron microscopy. The oral administration of powdered chow containing 0.02%-PFOA and PFBA to male rats of the Sprague-Dawley strain for 2 weeks and the single intraperitoneal injection of corn oil mixed with PFDA, PFOA, and PFOL at the dose of 100 mg/kg induced peroxisome proliferation markedly. PFOL, which has two hydrogen atoms around the hydroxylated carbon, should be metabolized to PFOA, which is an active inducer. Perfluorinated paraffins, PFD and PFO, did not show any induction, indicating the importance of the carboxylic group in the molecule for the peroxisome proliferation. Although the participation of thyroid hormone cannot be excluded, PFOA appears to act directly on the liver.				●						-		B	B
1405	実験動物（肝毒性）	Kennedy, G L Jr	Increase in mouse liver weight following feeding of ammonium perfluorooctanoate and related fluorochemicals	1987	Toxicol Lett. 1987 Dec;39(2-3):295-300. doi: 10.1016/0378-4274(87)90245-1.	The weight of the mouse liver following feeding of ammonium perfluorooctanoate, ammonium perfluorononanoate, Telomer B ammonium sulfate, and WG-III was increased in a dose-dependent manner. Dietary levels of 3 ppm or greater ammonium perfluorooctanoate for either 14 or 21 days produced a significant elevation in liver weight both on an absolute and on an organ/body weight ratio basis. Similarly, ammonium perfluorononanoate produced significant increases at the lowest level tested, 3 ppm. Telomer B ammonium sulfate and WG-III also produced liver weight increases but at higher feeding levels. The striking increase in liver weight following relatively short-term exposures in mice makes this a useful screening test for comparing the liver-enlarging capacity of ammonium perfluorooctanoate and related fluorochemicals.				●		●				-		B	B
1406	実験動物（肝毒性）	Kudo, N; Kawashima, Y	Fish oil-feeding prevents perfluorooctanoic acid-induced fatty liver in mice	1997	Toxicol Appl Pharmacol. 1997 Aug;145(2):285-93. doi: 10.1006/taap.1997.8186.	The effects of perfluorooctanoic acid (PFOA) on the levels of lipids in liver and serum were compared between mice fed a diet supplemented with soy bean oil (SO), perilla oil (PO), or fish oil (FO) for 4 weeks. Hepatic content of triglyceride (TG) was significantly lower in the mice fed the FO diet than that in the mice fed either the SO or the PO diet. The treatment with PFOA caused a marked accumulation of TG in the livers of SO-fed and PO-fed mice (seven- and twofold over their respective controls), whereas a level of TG remained low in the mice fed the FO diet. Incorporation in vivo of [3H]glycerol revealed that FO-feeding reduced synthesis of TG in the liver. The administration of PFOA increased the incorporation of [3H]glycerol into hepatic phospholipid (PL) regardless of the dietary oil, while synthesis of hepatic TG from [3H]glycerol was not altered by the treatment with PFOA. Serum level of TG was reduced by the administration of PFOA to the mice fed either the SO diet or the PO diet, while no change in the level was observed in the mice fed the FO diet. These results suggest that the accumulation of TG in the livers of PFOA-treated mice is due to the inhibition of the secretion of TG into circulation. PFOA-induced hepatic accumulation of TG is prevented by the feeding of the FO diet which inhibits TG formation. Among three dietary oils, FO-feeding alone prevented the PFOA-caused accumulation of TG in the liver. The importance of docosahexaenoic acid (22:6(n - 3)) is discussed in relation to the prevention of fatty liver induced by chemicals.				●						-		D	B
1407	実験動物（肝毒性）	Kudo, Naomi; Kawashima, Yoichi	Induction of triglyceride accumulation in the liver of rats by perfluorinated fatty acids with different carbon chain lengths: Comparison with induction of peroxisomal ß-oxidation	2003	Biol Pharm Bull. 2003 Jan;26(1):47-51. doi: 10.1248/bpb.26.47.	The potency to accumulate triglyceride (TG) was compared between perfluorinated fatty acids (PFCAs) with different carbon chain lengths in the liver of male and female rats and induction of peroxisomal beta-oxidation. In male rats, either perfluoroheptanoic acid (C7) or perfluorooctanoic acid (C8) had no effect, although perfluorononanonic acid (C9) and perfluorodecanoic acid (C10) markedly accumulated TG. In female rats, C7, C8, and C9 did not cause TG accumulation, whereas C10 caused TG accumulation at the same level as in male rats. TG accumulation induced by C9 was regulated by the level of testosterone in male rats. In contrast with TG accumulation, peroxisomal beta-oxidation was induced by C8, C9, and C10 in male rats and by C9 and C10 in female rats. Only a slight difference was observed in the induction by C9 between male and female rats. The induction of TG accumulation by these PFCAs occurred in a dose-dependent manner and significantly correlated with hepatic concentrations of PFCA regardless of their carbon chain length, as was observed with induction of peroxisomal beta-oxidation. There is, however, a striking difference in the hepatic concentration of PFCA required to cause induction of TG accumulation and that of peroxisomal beta-oxidation. The concentration of PFCA required to induce TG accumulation is much higher than that to induce peroxisomal beta-oxidation. These results strongly suggest that TG accumulation induced by PFCAs, as well as the induction of peroxisomal beta-oxidation, is dependent only on the number of PFCA molecules in hepatocytes, but is not due to the difference in their chemical structures, and that there is a marked difference in the PFCA threshold to cause distinct biological effects.				●						-		B	B
1408	実験動物（肝毒性）	Kudo, N; Mizuguchi, H; Yamamoto, A; Kawashima, Y	Alterations by perfluorooctanoic acid of glycerolipid metabolism in rat liver	1999	Chem Biol Interact. 1999 Mar 1;118(1):69-83. doi: 10.1016/s0009-2797(99)00002-2.	The effects of perfluorooctanoic acid (PFOA) feeding on hepatic levels of glycerolipids and the underlying mechanism were investigated. Feeding of rats with 0.01% of PFOA in the diet for 1 week caused an increase in the contents of phosphatidylcholine (PtdCho), phosphatidylethanolamine (PtdEtn), phosphatidylinositol (PtdIns), phosphatidylserine (PtdSer) and triglyceride (TG), which were 2.2, 2.4, 2.4, 1.6 and 5.2 times over control, respectively, on the basis of whole liver. The activities of glycerol-3-phosphate acyltransferase, diacylglycerol kinase and PtdSer decarboxylase were significantly increased upon PFOA feeding, whereas the activities of CTP:phosphoethanolamine cytidylyltransferase and PtdEtn N-methyltransferase were decreased. On the other hand, the activity of CTP:phosphocholine cytidylyltransferase was not increased by PFOA. Upon PFOA feeding, hepatic level of 16:0-18:1 PtdCho was markedly increased and, by contrast, the levels of molecular species of PtdCho which contain 18:2 were decreased, resulting in the reduced concentration of molecular species of serum PtdCho containing 18:2. The increase in the level of hepatic 16:0-18:1 PtdCho seemed to be due to 3-fold increase in the activities of both delta9 desaturase and 1-acylglycerophosphocholine (1-acyl-GPC) acyltransferase. The mechanism by which PFOA causes the accumulation of glycerolipids in liver was discussed.				●						-		B	B
1409	実験動物（肝毒性）	Pastoor, T P; Lee, K P; Perri, M A; Gillies, P J	Biochemical and morphological studies of ammonium perfluorooctanoate-induced hepatomegaly and peroxisome proliferation	1987	Exp Mol Pathol. 1987 Aug;47(1):98-109. doi: 10.1016/0014-4800(87)90011-6.	Ammonium perfluorooctanoate (APFO) is known to induce a striking hepatomegaly in rats. The purpose of these studies was to determine the causes of the hepatomegaly and compare the effect to other liver-enlarging compounds. Since the total hepatic DNA content was similar in control and APFO-treated rats, the hepatomegaly represented a hypertrophic rather than a hyperplastic response. The cytochrome P-450 content and activity of benzphetamine N-demethylase increased in the livers of APFO-treated rats, indicating the proliferation of the smooth endoplasmic reticulum. In contrast to the membrane-bound enzymes, the soluble enzymes glutathione S-transferase and UDPglucuronyltransferase were unaffected by APFO treatment. The activity of carnitine acetyltransferase was disproportionately increased relative to carnitine palmitoyltransferase in the livers of APFO vs that in control rats, confirming the predominant proliferation of peroxisomes vs that of mitochondria. Morphological studies confirmed the proliferation of the endoplasmic reticulum, mitochondria, and peroxisomes in the livers of APFO-treated rats. In contrast to many other peroxisome proliferating agents, APFO did not possess hypolipidemic activity.				●						-		D	B
1410	実験動物（肝毒性）	Peters, Jeffrey M; Gonzalez, Frank J	Why toxic equivalency factors are not suitable for perfluoroalkyl chemicals	2011	Chem Res Toxicol. 2011 Oct 17;24(10):1601-9. doi: 10.1021/tx200316x. Epub 2011 Sep 28.	The pervasive nature of perfluoroalkyl chemicals in the environment has generated considerable interest for developing new strategies for risk assessment. In experimental animal models, exposure to perfluoroalkyl chemicals can cause developmental toxicity and hepatotoxicity. Peroxisome proliferator-activated receptor-α (PPARα) is required to mediate some but not all of these effects. Since PPARα has a role in mediating some of these effects, and there is some overlap in the type of toxicities elicited by perfluoroalkyl chemicals, it has been suggested that a scaling system analogous to the toxic equivalency factor (TEF) system used for polychlorinated dibenzo-p-dioxins (PCDD), polychlorinated dibenzofurans (PCDF), and polychlorinated biphenyls (PCB) could be used for perfluoroalkyl chemicals. However, evidence suggests that perfluoroalkyl chemicals can activate/interfere with other receptors, and there is reason to suggest the possibility of species differences in the response mediated by different receptors as well as qualitative differences in toxicities elicited by perfluoroalkyl chemicals. These differences and other data gaps preclude the development of a TEF approach for perfluoroalkyl chemicals.				●	●					-		B	B
1411	実験動物（肝毒性）	Qazi, Mousumi Rahman; Hassan, Moustapha; Nelson, B Dean; Depierre, Joseph W; Abedi-Valugerdi, Manuchehr	Sub-acute, moderate-dose, but not short-term, low-dose dietary pre-exposure of mice to perfluorooctanoate aggravates concanavalin A-induced hepatitis	2013	Toxicol Lett. 2013 May 10;219(1):1-7. doi: 10.1016/j.toxlet.2013.02.017. Epub 2013 Mar 1.	Exposure of mice to perfluorooctanoate (PFOA) evokes pronounced hepatomegaly along with significant alterations in both the histological structure and immune status of the liver. The present study was designed to evaluate the effects of this perfluorochemical on immune-mediated liver damage. In this connection, the influence of both sub-acute (10 days), moderate-dose (0.002% w/w=3±0.7mg/kg body weight/day) and short-term (28 days), low-dose (0.00005% w/w=70±2μg/kg body weight/day) dietary pretreatment with PFOA on the development of concanavalin A (Con A)-induced liver damage in mice was examined. With sub-acute, moderate, but not short-term, low-dose exposure, PFOA aggravated the acute liver damage caused by Con A, i.e., elevated serum levels of transaminases and led to more pronounced damage of hepatic tissue. This aggravation was associated with significantly enhanced hepatic level of interleukin-6 (IL-6), but unaltered hepatic levels of tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ) and interleukin-4 (IL-4). Moreover, hepatic DNA fragmentation was not changed by sub-acute exposure to the moderate-dose. Our findings imply that exposure to PFOA may sensitize hepatic parenchymal cells to other toxicants that activate the hepatic immune system and thereby aggravate liver injury during acute inflammation.				●					●	-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①抽出	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1412	実験動物（肝毒性）	Rosen, Mitchell B; Abbott, Barbara D; Wolf, Douglas C; Corton, J Christopher; Wood, Carmen R; Schmid, Judith E; Das, Kaberi P; Zehr, Robert D; Blair, Eric T; Lau, Christopher	Gene profiling in the livers of wild-type and PPARα-null mice exposed to perfluorooctanoic acid	2008	Toxicol Pathol. 2008 Jun;36(4):592-607. doi: 10.1177/0192623308318208. Epub 2008 May 8.	Health concerns have been raised because perfluorooctanoic acid (PFOA) is commonly found in the environment and can be detected in humans. In rodents, PFOA is a carcinogen and a developmental toxicant. PFOA is a peroxisome proliferator-activated receptor alpha (PPARalpha) activator; however, PFOA is capable of inducing heptomegaly in the PPARalpha-null mouse. To study the mechanism associated with PFOA toxicity, wild-type and PPARalpha-null mice were orally dosed for 7 days with PFOA (1 or 3 mg/kg) or the PPARalpha agonist Wy14,643 (50 mg/kg). Gene expression was evaluated using commercial microarrays. In wild-type mice, PFOA and Wy14,643 induced changes consistent with activation of PPARalpha. PFOA-treated wild-type mice deviated from Wy14,643-exposed mice with respect to genes involved in xenobiotic metabolism. In PFOA-treated null mice, changes were observed in transcripts related to fatty acid metabolism, inflammation, xenobiotic metabolism, and cell cycle regulation. Hence, a component of the PFOA response was found to be independent of PPARalpha. Although the signaling pathways responsible for these effects are not readily apparent, overlapping gene regulation by additional PPAR isoforms could account for changes related to fatty acid metabolism and inflammation, whereas regulation of xenobiotic metabolizing genes is suggestive of constitutive androstane receptor activation.				●		●					-		B	B
1413	実験動物（肝毒性）	Rosen, M. B.; Schmid, J. R.; Corton, J. C.; Zehr, R. D.; Das, K. P.; Abbott, B. D.; Lau, C.	Gene expression profiling in wild-type and PPARα-null mice exposed to perfluorooctane sulfonate reveals PPARα-independent effects	2010	PPAR Research. Volume 2010. Article ID 794739. doi: 10.1155/2010/794739	Perfluorooctane sulfonate (PFOS) is a perfluoroalkyl acid (PFAA) and a persistent environmental contaminant found in the tissues of humans and wildlife. Although blood levels of PFOS have begun to decline, health concerns remain because of the long half-life of PFOS in humans. Like other PFAAs, such as, perfluorooctanoic acid (PFOA), PFOS is an activator of peroxisome proliferator-activated receptor-alpha (PPARα) and exhibits hepatocarcinogenic potential in rodents. PFOS is also a developmental toxicant in rodents where, unlike PFOA, its mode of action is independent of PPARα. Wild-type (WT) and PPARα-null (Null) mice were dosed with 0, 3, or 10 mg/kg/day PFOS for 7 days. Animals were euthanized, livers weighed, and liver samples collected for histology and preparation of total RNA. Gene profiling was conducted using Affymetrix 430_2 microarrays. In WT mice, PFOS induced changes that were characteristic of PPARα transactivation including regulation of genes associated with lipid metabolism, peroxisome biogenesis, proteasome activation, and inflammation. PPARα-independent changes were indicated in both WT and Null mice by altered expression of genes related to lipid metabolism, inflammation, and xenobiotic metabolism. Such results are similar to studies done with PFOA and are consistent with modest activation of the constitutive androstane receptor (CAR), and possibly PPARγ and/or PPARβ/δ. Unique treatment-related effects were also found in Null mice including altered expression of genes associated with ribosome biogenesis, oxidative phosphorylation, and cholesterol biosynthesis. Of interest was up-regulation of Cyp7a1, a gene which is under the control of various transcription regulators. Hence, in addition to its ability to modestly activate PPARα, PFOS induces a variety of PPARα-independent effects as well.				●	●						MOA（PPAR）→実験動物	1	B	A
1414	実験動物（肝毒性）	Shipley JM, Hurst CH, Tanaka SS, et al.	trans-Activation of PPAR(beta) and induction of PPAR(beta) target genes by perfluorooctane-based chemicals	2004	Toxicol Sci. 80(1):151-160. doi: 10.1093/toxsci/kfh130. Epub 2004 Apr 7.	Peroxisome proliferator-activated receptors (PPARs) are ligand-dependent transcription factors that activate target genes involved in lipid metabolism, energy homeostasis, and cell differentiation in response to diverse compounds, including environmental chemicals. The liver-expressed receptor PPARalpha mediates peroxisome proliferative responses associated with rodent hepatocarcinogenesis. Previous studies have established that certain perfluorooctanesulfonamide-based chemicals (PFOSAs) alter lipid metabolism, are hepatic peroxisome proliferators, and induce hepatocellular adenoma formation in rodents, suggesting that they activate PPARalpha. The present study investigates this question and characterizes the activation of mouse and human PPARalpha by PFOSAs. Perfluorooctanesulfonate (PFOS), an end-stage metabolite common to several PFOSAs, was found to activate both mouse and human PPARalpha in a COS-1 cell-based luciferase reporter trans-activation assay. Half-maximal activation (EC50) occurred at 13-15 microM PFOS, with no significant difference in the responsiveness of mouse and human PPARalpha. Mouse and human PPARalpha were activated by perfluorooctanesulfonamide (FOSA) over a similar concentration range; however, cellular toxicity precluded an accurate determination of EC50 values. Studies of 2-N-ethylperfluorooctanesulfonamido ethanol were less informative due to its insolubility. These findings were verified in an FAO rat hepatoma cell line that stably expresses PPARalpha, where the endogenous PPARalpha target genes peroxisomal bifunctional enzyme and peroxisomal 3-ketoacyl-CoA thiolase were activated up to approximately 10-20-fold by PFOS and FOSA. The interactions of PPARalpha with PFOS and FOSA, and the potential of these chemicals for activation of unique sets of downstream target genes, may help explain the diverse biological effects exhibited by PFOSAs and may aid in the evaluation of human and environmental risks associated with exposure to this important class of fluorochemicals.				●							-		B	B
1415	実験動物（肝毒性）	Son, Hee-Young; Kim, Sang-Hyun; Shin, Hong-In; Bae, Han Ik; Yang, Jae-Ho	Perfluorooctanoic acid-induced hepatic toxicity following 21-day oral exposure in mice	2008	Arch Toxicol. 2008 Apr;82(4):239-46. doi: 10.1007/s00204-007-0246-x. Epub 2007 Sep 14.	Perfluorooctanoic acid (PFOA) is a member of the perfluoroalkyl acids that have wide commercial applications and is a widespread pollutant of toxicological importance that has been detected in environmental matrices. The NOAEL and LOAEL of PFOA in rodent were reported 1 and 10 ppm, respectively. The current study characterizes the hepatic toxicities of PFOA in mice. Male ICR mice were exposed continuously to 0, 2, 10, 50 and 250 ppm of PFOA in drinking water for 21 days. Food and water consumption decreased in mice exposed to 250 ppm of PFOA. Mean body weight gain was reduced in mice exposed to 50 and 250 ppm of PFOA. The size and relative weight of the liver increased dose-dependently in PFOA-treated mice. Serum enzyme activities, alanine aminotransferase and aspartate aminotransferase, increased in mice exposed to PFOA in a dose-dependent manner. In the histopathological evaluation, the liver of PFOA-treated mice showed remarkable hepatocytomegaly and acidophilic cytoplasm. At the high doses of PFOA, diffuse hepatic damage by multifocal coagulation and liquefaction necrosis were noted. In contrast to the remarkable change of liver, the kidney had little change. The size and relative weights of the kidney, biomarkers of kidney damage (blood urea nitrogen, creatinine), and histopathological changes had no differences between PFOA-untreated and PFOA-treated mice. In conclusion, our results demonstrate that PFOA causes a toxic effect on the liver but not to the kidney.				●		●			●		-	1	A	B
1416	実験動物（肝毒性）	Starkov, A A; Wallace, K B	Structural determinants of fluorochemical-induced mitochondrial dysfunction	2002	Toxicol Sci. 2002 Apr;66(2):244-52. doi: 10.1093/toxsci/66.2.244.	Perfluorooctanoate (PFOA) and perfluorooctanesulfonate (PFOS) are thought to induce peroxisome proliferation and interfere with mitochondrial metabolic pathways. Direct measurements revealed that PFOA and the unsubstituted sulfonamide of perfluorooctane (FOSA) uncouple mitochondrial respiration by increasing proton conductance. The purpose of this investigation was to characterize structural determinants responsible for the mitochondrial uncoupling effect of several structurally related fluorochemicals. Included in the study were PFOA, PFOS, FOSA, the N-acetate of FOSA (perfluorooctanesulfonamidoacetate, FOSAA), N-ethylperfluorooctanesulfonamide (N-EtFOSA), and the N-ethyl alcohol [2-(N-ethylperfluorooctanesulfonamido)ethyl alcohol, N-EtFOSE] and N-acetic acid (N-ethylperfluorooctanesulfonamidoacetate, N-EtFOSAA) of N-EtFOSA. Each test compound was dissolved in ethanol and added directly to an incubation medium containing substrate-energized rat liver mitochondria. Mitochondrial respiration and membrane potential were measured concurrently using an oxygen electrode and a TPP+ -selective electrode, respectively. All of the compounds tested, at sufficiently high concentrations, had the capacity to interfere with mitochondrial respiration, albeit via different mechanisms and with varying potencies. At sufficiently high concentrations, the free acids PFOA and PFOS caused a slight increase in the intrinsic proton leak of the mitochondrial inner membrane, which resembled a surfactant-like change in membrane fluidity. Similar effects were observed with the sulfonamide N-EtFOSE. Another fully substituted sulfonamide, N-EtFOSAA, at high concentrations caused inhibition of respiration, the release of cytochrome c, and high-amplitude swelling of mitochondria. The swelling was prevented by cyclosporin A or by EGTA, indicating that this compound induced the mitochondrial permeability transition. The unsubstituted and mono-substituted amides FOSA, N-EtFOSA, and FOSAA all exerted a strong uncoupling effect on mitochondria resembling that of protonophoric uncouplers. Among these compounds, FOSA was a very potent uncoupler of oxidative phosphorylation, with an IC50 of approximately 1 microM. These data suggest that the protonated nitrogen atom with a favorable pKa is essential for the uncoupling action of perfluorooctane sulfonamides in mitochondria, which may be critical to the mechanism by which these compounds interfere with mitochondrial metabolism to induce peroxisome proliferation in vivo.				●							-		D	B
1417	実験動物（肝毒性）	Takacs, Margy L; Abbott, Barbara D	Activation of mouse and human peroxisome proliferator-activated receptors (a, b/d, c) by perfluorooctanoic acid and perfluorooctane sulfonate	2007	Toxicol Sci. 2007 Jan;95(1):108-17. doi: 10.1093/toxsci/kfl135. Epub 2006 Oct 17.	This study evaluates the potential for perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) to activate peroxisome proliferator-activated receptors (PPARs), using a transient transfection cell assay. Cos-1 cells were cultured in Dulbecco's Minimal Essential Medium (DMEM) with fetal bovine serum in 96-well plates and transfected with mouse or human PPARalpha, beta/delta, or gamma reporter plasmids. Transfected cells were exposed to PFOA (0.5-100 microM), PFOS (1-250 microM), positive controls (i.e., known agonists and antagonists), and negative controls (i.e., DMEM, 0.1% water, and 0.1% dimethyl sulfoxide). Following treatment for 24 h, activity was measured using the Luciferase reporter assay. In this assay, PFOA had more transactivity than PFOS with both the mouse and human PPAR isoforms. PFOA significantly increased mouse and human PPARalpha and mouse PPARbeta/delta activity relative to vehicle. PFOS significantly increased activation of mouse PPARalpha and PPARbeta/delta isoforms. No significant activation of mouse or human PPARgamma was observed with PFOA or PFOS. The PPARalpha antagonist, MK-886, significantly suppressed PFOA and PFOS activity of mouse and human PPARalpha. The PPARgamma antagonist, GW9662, significantly suppressed PFOA activity on the human isoform. In conclusion, this study characterized the dose response and differential activation of mouse and human PPARalpha, beta/delta, gamma by PFOA and PFOS. While this model allows opportunities to compare potential activation by perfluoroalkyl acids, it only evaluates the interaction and activation of the PPAR reporter constructs and is not necessarily predictive of a toxicological response in vivo.				●	●						-		D	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①D	文献クラン②B
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1418	実験動物（肝毒性）	Vanden Heuvel, J P; Kuslikis, B I; Shrago, E; Peterson, R E	Inhibition of long-chain acyl-CoA synthetase by the peroxisome proliferator perfluorodecanoic acid in rat hepatocytes	1991	Biochem Pharmacol. 1991 Jul 5;42(2):295-302. doi: 10.1016/0006-2952(91)90716-i.	Perfluorodecanoic acid (PFDA) is a potent peroxisome proliferator and is known to affect hepatic lipid metabolism in rats. The effects of PFDA on fatty acid utilization were examined in isolated rat hepatocyte suspensions and in rat liver mitochondria and microsomes. PFDA inhibited the oxidation of palmitic acid but not octanoic or pyruvic acids when hepatocytes were incubated with 1 mM PFDA. At this PFDA concentration the esterification of palmitic acid into triacylglycerols was also reduced. The activity of long-chain acyl-CoA synthetase (ACS), an enzyme essential for both oxidation and esterification of fatty acids, was reduced in hepatocytes incubated with 1 mM PFDA. Carnitine palmitoyltransferase (CPT), an important enzyme for the oxidation of long-chain fatty acids, was not altered in hepatocytes incubated with this PFDA concentration. In rat liver mitochondria, palmitate oxidation and ACS activity were reduced significantly (P less than 0.01) at a PFDA concentration that had no effect on CPT activity. The inhibition of ACS by PFDA was similar in liver mitochondria and microsome preparations. In mitochondria incubated with PFDA, the inhibition of ACS appears to be noncompetitive for the substrates palmitic acid and CoA. However, the ACS inhibition by PFDA appeared to be competitive for the ATP binding site of the enzyme. Several chain length perfluorinated fatty acids were examined for their ability to inhibit mitochondrial ACS. Short-chain perfluorinated fatty acids (perfluoropropionic and -butyric acid) did not inhibit ACS activity. However, medium-chain perfluorinated acids (perfluorooctanoic, -ananoic and -decanoic acid) were found to be potent inhibitors of ACS in isolated mitochondria. Whether ACS inhibition is causally related to PFDA-induced peroxisome proliferation and altered lipid metabolism seen in vivo is yet to be determined.				●						-		D	B
1419	実験動物（肝毒性）	Vanden Heuvel, John P; Thompson, Jerry T; Frame, Steven R; Gillies, Peter J	Differential activation of nuclear receptors by perfluorinated fatty acid analogs and natural fatty acids: A comparison of human, mouse, and rat peroxisome proliferator-activated receptor-α, -ß, and -γ, liver x receptor-ß, and retinoid x receptor-α	2006	Toxicol Sci. 2006 Aug;92(2):476-89. doi: 10.1093/toxsci/kfl014. Epub 2006 May 26.	Administration of ammonium salts of perfluorooctanoate (PFOA) to rats results in peroxisome proliferation and benign liver tumors, events associated with activation of the nuclear receptor (NR) peroxisome proliferator-activated receptor-alpha (PPARalpha). Due to its fatty acid structure, PFOA may activate other NRs, such as PPARbeta, PPARgamma, liver X receptor (LXR), or retinoid X receptor (RXR). In this study, the activation of human, mouse, and rat PPARalpha, PPARbeta, PPARgamma, LXRbeta, and RXRalpha by PFOA (including its linear and branched isomers) and perfluorooctane sulfonate (PFOS) was investigated and compared to several structural classes of natural fatty acids and appropriate positive control ligands. An NR ligand-binding domain/Gal4 DNA-binding domain chimeric reporter system was used. Human, mouse, and rat PPARalpha were activated by PFOA isomers and PFOS. PPARbeta was less sensitive to the agents tested, with only PFOA affecting the mouse receptor. PFOA and PFOS also activated human, mouse, and rat PPARgamma, although the maximum induction of PPARgamma was much less than that seen with rosiglitazone, suggesting that PFOA and PFOS are partial agonists of this receptor. Neither LXRbeta nor the common heterodimerization partner RXRalpha was activated by PFOA in any species examined. Taken together, these data show that of the NRs studied, PPARalpha is the most likely target of PFOA and PFOS, although PPARgamma is also activated to some extent. Compared to naturally occurring long-chain fatty acids, e.g. linoleic and alpha-linolenic acids, these perfluorinated fatty acid analogs were more selective and less potent in their activation of the NRs.				●		●				-		D	B
1420	実験動物（肝毒性）	Wallace, K B; Kissling, G E; Melnick, R L; Blystone, C R	Structure-activity relationships for perfluoroalkane-induced in vitro interference with rat liver mitochondrial respiration	2013	Toxicol Lett. 2013 Oct 9;222(3):257-64. doi: 10.1016/j.toxlet.2013.07.025. Epub 2013 Aug 14.	Perfluorinated alkyl acids (PFAAs) represent a broad class of commercial products designed primarily for the coatings industry. However, detection of residues globally in a variety of species led to the discontinuation of production in the U.S. Although PFAAs cause activation of the PPARα and CAR nuclear receptors, interference with mitochondrial bioenergetics has been implicated as an alternative mechanism of cytotoxicity. Although the mechanisms by which the eight carbon chain PFAAs interfere with mitochondrial bioenergetics are fairly well described, the activities of the more highly substituted or shorter chain PFAAs are far less well characterized. The current investigation was designed to explore structure-activity relationships by which PFAAs interfere with mitochondrial respiration in vitro. Freshly isolated rat liver mitochondria were incubated with one of 16 different PFAAs, including perfluorinated carboxylic, acetic, and sulfonic acids, sulfonamides and sulfamido acetates, and alcohols. The effect on mitochondrial respiration was measured at five concentrations and dose-response curves were generated to describe the effects on state 3 and 4 respiration and respiratory control. With the exception of PFOS, all PFAAs at sufficiently high concentrations (>20μM) stimulated state 4 and inhibited state 3 respiration. Stimulation of state 4 respiration was most pronounced for the carboxylic acids and the sulfonamides, which supports prior evidence that the perfluorinated carboxylic and acetic acids induce the mitochondrial permeability transition, whereas the sulfonamides are protonophoric uncouplers of oxidative phosphorylation. In both cases, potency increased with increasing carbon number, with a prominent inflection point between the six and eight carbon congeners. The results provide a foundation for classifying PFAAs according to specific modes of mitochondrial activity and, in combination with toxicokinetic considerations, establishing structure-activity-based boundaries for initial estimates of risk for noncancer endpoints for PFAAs for which minimal in vivo toxicity testing currently exists.				●						-		D	B
1421	実験動物（肝毒性）	Walters, M W; Bjork, J A; Wallace, K B	Perfluorooctanoic acid stimulated mitochondrial biogenesis and gene transcription in rats	2009	Toxicology. 2009 Oct 1;264(1-2):10-5. doi: 10.1016/j.tox.2009.07.003. Epub 2009 Jul 16.	Perfluorooctanoic acid (PFOA), used in the production of non-stick surface compounds, exhibits a worldwide distribution in the serum of humans and wildlife. In rodents PFOA transactivates PPARalpha and PPARgamma nuclear receptors and increases mitochondrial DNA (mtDNA) copy number, which may be critical to the altered metabolic state of affected animals. A key regulator of mitochondrial biogenesis and transcription of mitochondrial genes is the PPARgamma coactivator-1alpha (Pgc-1alpha) protein. The purpose of this study was to determine if Pgc-1alpha is implicated in the stimulation of mitochondrial biogenesis that occurs following the treatment of rats with PFOA. Livers from adult male Sprague-Dawley rats that received a 30 mg/kg daily oral dose of PFOA for 28 days were used for all experiments. Analysis of mitochondrial replication and transcription was performed by real time PCR, and proteins were detected using western blotting. PFOA treatment caused a transcriptional activation of the mitochondrial biogenesis pathway leading to a doubling of mtDNA copy number. Further, transcription of OXPHOS genes encoded by mtDNA was 3-4 times greater than that of nuclear encoded genes, suggestive of a preferential induction of mtDNA transcription. Western blot analysis revealed an increase in Pgc-1alpha, unchanged Tfam and decreased Cox II and Cox IV subunit protein expression. We conclude that PFOA treatment in rats induces mitochondrial biogenesis at the transcriptional level with a preferential stimulation of mtDNA transcription and that this occurs by way of activation of the Pgc-1alpha pathway. Implication of the Pgc-1alpha pathway is consistent with PPARgamma transactivation by PFOA and reveals new understanding and possibly new critical targets for assessing or averting the associated metabolic disease.				●						-		D	B
1422	実験動物（肝毒性）	Wolf, Cynthia J; Rider, Cynthia V; Lau, Christopher; Abbott, Barbara D	Evaluating the additivity of perfluoroalkyl acids in binary combinations on peroxisome proliferator-activated receptor-alpha activation	2014	Toxicology. 2014 Feb 28;316:43-54. doi: 10.1016/j.tox.2013.12.002. Epub 2013 Dec 26.	Perfluoroalkyl acids (PFAAs) are found globally in the environment, detected in humans and wildlife, and are typically present as mixtures of PFAA congeners. Mechanistic studies have found that responses to PFAAs are mediated in part by PPARα. Our previous studies showed that individual PFAAs activate PPARα transfected into COS-1 cells. The goal of the current study was to determine if binary combinations of perfluorooctanoic acid (PFOA) and another PFAA act in an additive fashion to activate PPARα in the mouse one-hybrid in vitro model. COS-1 cells were transiently transfected with mouse PPARα luciferase reporter construct and exposed to either vehicle control (0.1% DMSO or water), PPARα agonist (WY14643, 10 μM), PFOA at 1-128μM, perfluorononanoic acid (PFNA) at 1-128 μM, perfluorohexanoic acid (PFHxA) at 8-1024 μM, perfluorooctane sulfonate (PFOS) at 4-384 μM or perfluorohexane sulfonate (PFHxS) at 8-2048 μM to generate sigmoidal concentration-response curves. In addition, cells were exposed to binary combinations of PFOA+either PFNA, PFHxA, PFOS or PFHxS in an 8×8 factorial design. The concentration-response data for individual chemicals were fit to sigmoidal curves and analyzed with nonlinear regression to generate EC_{50}s and Hillslopes, which were used in response-addition and concentration-addition models to calculate predicted responses for mixtures in the same plate. All PFOA+PFAA combinations produced concentration-response curves that were closely aligned with the predicted curves for both response addition and concentration addition at low concentrations. However, at higher concentrations of all chemicals, the observed response curves deviated from the predicted models of additivity. We conclude that binary combinations of PFAAs behave additively at the lower concentration ranges in activating PPARα in this in vitro system.				●		●				-		B	B
1423	実験動物（肝毒性）	Wolf, Cynthia J; Takacs, Margy L; Schmid, Judith E; Lau, Christopher; Abbott, Barbara D	Activation of mouse and human peroxisome proliferator-activated receptor alpha by perfluoroalkyl acids of different functional groups and chain lengths	2008	Toxicol Sci. 2008 Nov;106(1):162-71. doi: 10.1093/toxsci/kfn166. Epub 2008 Aug 18.	Perfluoroalkyl acids (PFAAs) are surfactants used in consumer products and persist in the environment. Some PFAAs elicit adverse effects on rodent development and survival. PFAAs can activate peroxisome proliferator-activated receptor alpha (PPARalpha) and may act via PPARalpha to produce some of their effects. This study evaluated the ability of numerous PFAAs to induce mouse and human PPARalpha activity in a transiently transfected COS-1 cell assay. COS-1 cells were transfected with either a mouse or human PPARalpha receptor-luciferase reporter plasmid. After 24 h, cells were exposed to either negative controls (water or dimethyl sulfoxide, 0.1%); positive control (WY-14643, PPARalpha agonist); perfluorooctanoic acid or perfluorononanoic acid at 0.5-100 microM; perfluorobutanoic acid, perfluorohexanoic acid, perfluorohexane sulfonate, or perfluorodecanoic acid (PFDA) at 5-100 microM; or perfluorobutane sulfonate or perfluorooctane sulfonate at 1-250 microM. After 24 h of exposure, luciferase activity from the plasmid was measured. Each PFAA activated both mouse and human PPARalpha in a concentration-dependent fashion, except PFDA with human PPARalpha. Activation of PPARalpha by PFAA carboxylates was positively correlated with carbon chain length, up to C9. PPARalpha activity was higher in response to carboxylates compared to sulfonates. Activation of mouse PPARalpha was generally higher compared to that of human PPARalpha. We conclude that, in general, (1) PFAAs of increasing carbon backbone chain lengths induce increasing activity of the mouse and human PPARalpha with a few exceptions, (2) PFAA carboxylates are stronger activators of mouse and human PPARalpha than PFAA sulfonates, and (3) in most cases, the mouse PPARalpha appears to be more sensitive to PFAAs than the human PPARalpha in this model.				●						-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1424	実験動物（肝毒性）	Xie, Yi; Yang, Qian; Nelson, B Dean; DePierre, Joseph W	The relationship between liver peroxisome proliferation and adipose tissue atrophy induced by peroxisome proliferator exposure and withdrawal in mice	2003	Biochem Pharmacol. 2003 Sep 1;66(5):749-56. doi: 10.1016/s0006-2952(03)00386-1.	We have previously demonstrated that severe adipose tissue atrophy occurs upon dietary treatment of mice with potent peroxisome proliferators (PPs). This atrophy occurs subsequent to peroxisome proliferation in the liver and may represent a novel addition to the pleiotropic effects exerted by PPs. In the present study we have characterized the recovery of mice from such atrophy following cessation of exposure. Following termination of treatment with perfluorooctanoic acid (PFOA) for 7 days, the adipose tissue atrophy was rapidly reversed, beginning on 2-5 days of recovery and being complete within 10 days. In contrast, hepatic peroxisome proliferation recovered much more slowly, indicating that these processes are not strictly coordinated. Analysis of lipoprotein lipase and hormone-sensitive lipase activities in adipose tissue revealed that the decrease and increase in these activities, respectively, caused by PFOA were both reversed within 10 days of recovery. Overall, these data provide further support for our previous conclusion that the adipose tissue atrophy induced by PFOA is caused, at least in part, by changes in the activities of lipoprotein lipase and hormone-sensitive lipase. The serum level of cholesterol, which increased after termination of PFOA treatment, returned to normal with a time-course similar to the recovery of adipose tissue weight, although hepatic peroxisome proliferation was still present. The possible relationship between the reduction in serum cholesterol and/or in its availability to peripheral tissues and the associated atrophy of adipose tissues caused by PPs is discussed.				●						-		D	B
1425	実験動物（肝毒性）	Yang, Bei; Zou, Weiying; Hu, Zhenzhen; Liu, Fangming; Zhou, Ling; Yang, Shulong; Kuang, Haibin; Wu, Lei; Wei, Jie; Wang, Jinglei; Zou, Ting; Zhang, Dalei	Involvement of oxidative stress and inflammation in liver injury caused by perfluorooctanoic acid exposure in mice	2014	Biomed Res Int. 2014;2014:409837. doi: 10.1155/2014/409837. Epub 2014 Mar 2.	Perfluorooctanoic acid (PFOA) is widely present in the environment and has been reported to induce hepatic toxicity in animals and humans. In this study, mice were orally administered different concentrations of PFOA (2.5, 5, or 10 mg/kg/day). Histological examination showed that the exposure to PFOA for 14 consecutive days led to serious hepatocellular injury and obvious inflammatory cell infiltration. In addition, malondialdehyde formation and hydrogen peroxide generation, indicators of oxidative stress, were significantly induced by PFOA treatment in the liver of mice. Furthermore, hepatic levels of interleukin-6, cyclooxygenase-2, and C-reactive protein, markers of inflammatory response, were markedly increased by exposure to PFOA in mice. These results demonstrated that PFOA-induced hepatic toxicity may be involved in oxidative stress and inflammatory response in mice.				●					●	-	1	A	B
1426	実験動物（肝毒性）	Zhang, Lianying; Ren, Xiao-Min; Wan, Bin; Guo, Liang-Hong	Structure-dependent binding and activation of perfluorinated compounds on human peroxisome proliferator-activated receptor γ	2014	Toxicol Appl Pharmacol. 2014 Sep 15;279(3):275-283. doi: 10.1016/j.taap.2014.06.020. Epub 2014 Jul 3.	Perfluorinated compounds (PFCs) have been shown to disrupt lipid metabolism and even induce cancer in rodents through activation of peroxisome proliferator-activated receptors (PPARs). Lines of evidence showed that PPARα was activated by PFCs. However, the information on the binding interactions between PPARγ and PFCs and subsequent alteration of PPARγ activity is still limited and sometimes inconsistent. In the present study, in vitro binding of 16 PFCs to human PPARγ ligand binding domain (hPPARγ-LBD) and their activity on the receptor in cells were investigated. The results showed that the binding affinity was strongly dependent on their carbon number and functional group. For the eleven perfluorinated carboxylic acids (PFCAs), the binding affinity increased with their carbon number from 4 to 11, and then decreased slightly. The binding affinity of the three perfluorinated sulfonic acids (PFSAs) was stronger than their PFCA counterparts. No binding was detected for the two fluorotelomer alcohols (FTOHs). Circular dichroim spectroscopy showed that PFC binding induced distinctive structural change of the receptor. In dual luciferase reporter assays using transiently transfected Hep G2 cells, PFCs acted as hPPARγ agonists, and their potency correlated with their binding affinity with hPPARγ-LBD. Molecular docking showed that PFCs with different chain length bind with the receptor in different geometry, which may contribute to their differences in binding affinity and transcriptional activity.				●						-		B	B
1427	ヒト（肝毒性）	Borg, Daniel; Lund, Bert-Ove; Lindquist, Nils-Gunnar; Håkansson, Helen	Cumulative risk assessment of 17 perfluoroalkylated and polyfluoroalkylated substances (PFASs) in the Swedish population	2013	Environ Int. 2013 Sep;59:112-23. doi: 10.1016/j.envint.2013.05.009. Epub 2013 Jun 21.	Humans are simultaneously exposed to a multitude of chemicals. Human health risk assessment of chemicals is, however, normally performed on single substances, which may underestimate the total risk, thus bringing a need for reliable methods to assess the risk of combined exposure to multiple chemicals. Per- and polyfluoroalkylated substances (PFASs) is a large group of chemicals that has emerged as global environmental contaminants. In the Swedish population, 17 PFASs have been measured, of which the vast majority lacks human health risk assessment information. The objective of this study was to for the first time perform a cumulative health risk assessment of the 17 PFASs measured in the Swedish population, individually and in combination, using the Hazard Index (HI) approach. Swedish biomonitoring data (blood/serum concentrations of PFASs) were used and two study populations identified: 1) the general population exposed indirectly via the environment and 2) occupationally exposed professional ski waxers. Hazard data used were publicly available toxicity data for hepatotoxicity and reproductive toxicity as well as other more sensitive toxic effects. The results showed that PFASs concentrations were in the low ng/ml serum range in the general population, reaching high ng/ml and low μg/ml serum concentrations in the occupationally exposed. For those congeners lacking toxicity data with regard to hepatotoxicity and reproductive toxicity read-across extrapolations was performed. Other effects at lower dose levels were observed for some well-studied congeners. The risk characterization showed no concern for hepatotoxicity or reproductive toxicity in the general population except in a subpopulation eating PFOS-contaminated fish, illustrating that high local exposure may be of concern. For the occupationally exposed there was concern for hepatotoxicity by PFOA and all congeners in combination as well as for reproductive toxicity by all congeners in combination, thus a need for reduced exposure was identified. Concern for immunotoxicity by PFOS and for disrupted mammary gland development by PFOA was identified in both study populations as well as a need of additional toxicological data for many PFAS congeners with respect to all assessed endpoints.					●	●				-	1	B	A
1428	複合影響	Ding, Guanghui; Zhang, Jing; Chen, Yihong; Wang, Luyan; Wang, Man; Xiong, Deqi; Sun, Yeqing	Combined effects of PFOS and PFOA on zebrafish (Danio rerio) embryos	2013	Arch Environ Contam Toxicol. 2013 May;64(4):668-75. doi: 10.1007/s00244-012-9864-2. Epub 2013 Mar 12.	Perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) are two kinds of emerging contaminants most studied in recent years. However, there is limited information about their combined toxicity to aquatic organisms. In the present study, the single and combined toxicity of PFOA and PFOS to zebrafish (Danio rerio) embryos were investigated. PFOS was more toxic than PFOA for the single toxicity. In four mixtures, PFOS and PFOA showed complex interactive effects that changed from additive to synergistic effect, then to antagonistic effect, and at last turnover to synergic effect again, with increased molar ratios of PFOS. Neither the concentration-addition model nor the independent-action model could predict the combined effects when strong interactive effects existed. Although the interactive effects of PFOS and PFOA affected their combined toxicity, the trend of mixture toxicity still showed an increase with increasing molar ratios of PFOS in the mixture.					●	●				-		C	B
1429	実験動物（反復投与毒性）	Goldenthal, E.I., Jessup, D.C., Geil, R.G. and Mehring, J.S.	Ninety-day subacute rat toxicity study　Study No. 137-085.	1978	International Research and Development Corporation. [As cited in OECD (2002); EFSA (2008); Health Canada (2012)].	No abstract available					●				●	企業データ		D	D
1430	実験動物（肝毒性）	Kim, Hyung-Sub; Jun Kwack, Seung; Sik Han, Eui; Seok Kang, Tae; Hee Kim, Seung; Young Han, Soon	Induction of apoptosis and CYP4A1 expression in Sprague-Dawley rats exposed to low doses of perfluorooctane sulfonate	2011	J Toxicol Sci. 2011 Apr;36(2):201-10. doi: 10.2131/jts.36.201.	In previous studies, perfluorooctane sulfonate (PFOS), an environmental organic compound, was reported to cause hepatotoxicity and hypolipidemia in rodents. However, the low dose toxicity of PFOS and the toxic mechanisms involved remain to be determined. To clarify the low dose toxicity and action mechanism in the target organ toxicity, Sprague-Dawley (SD) rats were orally administered with PFOS at the doses of 0, 1.25, 5, 10 mg/kg/day for 28 days. As a result, no death or abnormal symptoms were observed in all groups. The significant loss of mean body weight was observed in female rats treated with 10 mg/kg PFOS and the relative liver weight of 10 mg/kg PFOS-treated group was significantly greater compared to control. Histopathological examination revealed that fatty change was evident in the liver of male rats treated with PFOS (5 and 10 mg/kg) and hypertrophy and cellular swellings in females at the dose of 10 mg/kg, which showed different pattern of pathological lesions. In addition, we demonstrated the expression induction of hepatic caspase-3 and cytochrome P450 4A1 (CYP4A1) related with apoptosis and lipid metabolism, respectively. This study suggested that no-observed-adverse-effect level (NOAEL) of PFOS was 1.25 mg/kg in 28-day repeated toxicity study and, however, the toxic response showed gender differences. The possible toxic mechanism of PFOS was the induction of apoptosis and altering lipid metabolism which resulted in hepatotoxicity.					●					-	1	A	B
1431	相加性	Ludwicki, Jan K; Góralczyk, Katarzyna; Struciński, Paweł; Wojtyniak, Bogdan; Rabczenko, Daniel; Toft, Gunnar; Lindh, Christian H; Jönsson, Bo A G; Lenters, Virissa; Heederik, Dick; Czaja, Katarzyna; Hernik, Agnieszka; Pedersen, Henning S; Zvyezday, Valentyna; Bonde, Jens Peter	Hazard quotient profiles used as a risk assessment tool for PFOS and PFOA serum levels in three distinctive European populations	2015	Environ Int. 2015 Jan;74:112-8. doi: 10.1016/j.envint.2014.10.001. Epub 2014 Oct 21.	Perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) blood levels are commonly used as biomarkers of human environmental exposure to these compounds. Many biomonitoring studies indicate 100% detection for PFOS and PFOA thus justifying a concern of possible risk for the most exposed individuals. This study addresses the predictive value of hazard quotients (HQs) calculated on the basis of serum PFOS and PFOA in male and female populations of reproductive age in Greenland, Poland and Ukraine. Overall, 2026 results of PFOS and PFOA serum concentrations (589 males, 1437 females) were obtained from the INUENDO database. HQs were calculated from the actual biomonitoring results and literature-based animal data linking toxicological outcomes and critical PFOS/PFOA serum levels. HQs for serum PFOS were calculated based on Points of Departure (PoD) at 13μgmL(-1) (cynomolgus monkeys, 183days, changes in THS and T3) and for PFOA at 7.1μgmL(-1) serum (male rats, 90days, hepatocellular necrosis, increased liver weight). Uncertainty factors were applied to reflect interspecies differences and human variability. Serum HQs were expressed as a ratio relative to the point of departure for each PFOS and PFOA. Only in the three cases of males in Greenland were there serum PFOS levels showing HQ values exceeding 1, so indicating that such serum levels may be of concern. The mean serum concentration of PFOS was significantly higher in male than in female populations. Despite significant differences between HQ profiles for PFOS and PFOA in donors from Greenland, Poland and Ukraine, the concentrations of these perfluoroalkylated compounds do not indicate a cause for concern, except for the three aforementioned cases from Greenland. This study demonstrates that the HQ approach can help to interpret human biomonitoring data and thus serve as a valuable tool in further risk assessment priority settings and may also be used as a basis for taking decisions in risk management.					●	●				-	1	D	A

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報抽出対象	文献ランク①	文献ランク②
1432	複合影響	Meek, M E Bette; Boobis, Alan R; Crofton, Kevin M; Heinemeyer, Gerhard; Raaij, Marcel Van; Vickers, Carolyn	Risk assessment of combined exposure to multiple chemicals: a WHO/IPCS framework	2011	Regul Toxicol Pharmacol. 2011 Apr 2. doi: 10.1016/j.yrtph.2011.03.010.	This paper describes a framework for the risk assessment of combined exposure to multiple chemicals based on and developed subsequent to the World Health Organization/International Programme on Chemical Safety Workshop on Aggregate/Cumulative Risk Assessment (Combined Exposures to Multiple Chemicals) held in 2007. The framework is designed to aid risk assessors in identifying priorities for risk management for a wide range of applications where co-exposures to multiple chemicals are expected. It is based on a hierarchical (phased) approach that involves integrated and iterative consideration of exposure and hazard at all phases, with each tier being more refined (i.e., less cautious and more certain) than the previous one, but more labor and data intensive. It includes reference to predictive and probabilistic methodology in various tiers in addition to tiered consideration of uncertainty. The paper also annexes two case studies that have been developed to test and refine the framework.					●	●				-		D	B
1433	実験動物（肝毒性）	NOTOX	Exploratory 28-day oral toxicity study with telomer alcohol, telomer acrylate, [redacted confidential business information], PFHS and PFOS (positive control) by daily gavage in the rat followed by a 14/28-day recovery period	1999	NOTOX. # 242933. [As cited in Health Canada (2006)].	No abstract available					●					企業データ		D	D
1434	相加性	Rodea-Palomares, Ismael; Leganés, Francisco; Rosal, Roberto; Fernández-Piñas, Francisca	Toxicological interactions of perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) with selected pollutants	2012	J Hazard Mater. 2012 Jan 30;201-202:209-18. doi: 10.1016/j.jhazmat.2011.11.061. Epub 2011 Nov 29.	The combined toxicity of the perfluorinated surfactants perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA) and several pollutants (Hg(2+), Cd(2+), 2,4-D, propylparaben, mitomycin C and furazolidone) has been examined with a bioluminescent cyanobacterial toxicity test. Hg(2+), Cd(2+), mitomycin C and furazolidone could be included in the "Acute aquatic hazard" category established in the Regulation (EC) No 1272/2008 being "very toxic to aquatic life". Toxicological interactions of PFOA, PFOS with these pollutants in binary, ternary and multicomponent mixtures were studied using the combination-index method. PFOA and PFOS showed an antagonistic interaction at the whole range of effect levels, this may explain in part the finding that PFOA and PFOS interacted in an inverse way with the organic pollutants; the relative hydrophobicity of the tested compounds would also explain this interaction pattern. The interaction of both PFOS and PFOA with heavy metals was mostly antagonistic, decreasing metal toxicity. With increasing complexity of the mixtures, the CI method predicted synergism at low to very low levels of effect; pollutant combinations at their mixture NOECs were tested and confirmed the predicted synergism.					●	●				-		C	B
1435	MOA（PPAR）	Rosen, Mitchell B; Das, Kaberi P; Wood, Carmen R; Wolf, Cynthia J; Abbott, Barbara D; Lau, Christopher	Evaluation of perfluoroalkyl acid activity using primary mouse and human hepatocytes	2013	Toxicology. 2013 Jun 7;308:129-37. doi: 10.1016/j.tox.2013.03.011. Epub 2013 Apr 6.	While perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) have been studied at length, less is known about the biological activity of other perfluoroalkyl acids (PFAAs) detected in the environment. Using a transient transfection assay developed in COS-1 cells, our group has previously evaluated a variety of PFAAs for activity associated with activation of peroxisome proliferator-activated receptor alpha (PPARα). Here we use primary heptatocytes to further assess the biological activity of a similar group of PFAAs using custom designed Taqman Low Density Arrays. Primary mouse and human hepatocytes were cultured for 48h in the presence of varying concentrations of 12 different PFAAs or Wy14,643, a known activator of PPARα. Total RNA was collected and the expression of 48 mouse or human genes evaluated. Gene selection was based on either in-house liver microarray data (mouse) or published data using primary hepatocytes (human). Gene expression in primary mouse hepatocytes was more restricted than expected. Genes typically regulated in whole tissue by PPARα agonists were not altered in mouse cells including Acox1, Me1, Acaa1a, Hmgcs1, and Slc27a1. Cyp2b10, a gene regulated by the constitutive androstane receptor and a transcript normally up-regulated by in vivo exposure to PFAAs, was also unchanged in cultured mouse hepatocytes. Cyp4a14, Ehhadh, Pdk4, Cpt1b, and Fabp1 were regulated as expected in mouse cells. A larger group of genes were differentially expressed in human primary hepatocytes, however, little consistency was observed across compounds with respect to which genes produced a significant dose response making the determination of relative biological activity difficult. This likely reflects weaker activation of PPARα in human versus rodent cells as well as variation among individual cell donors. Unlike mouse cells, CYP2B6 was up-regulated in human hepatocytes by a number of PFAAs as was PPARδ. Rankings were conducted on the limited dataset. In mouse hepatocytes, the pattern was similar to that previously observed in the COS-1 reporter cell assay. With the exception of PFHxA, longer chain PFAA carboxylates were the most active. The pattern was similar in human hepatocytes, although PFDA and PFOS showed higher activity than previously observed while PFOA showed somewhat less activity. These data reflect inherent challenges in using primary hepatocytes to predict toxicological response.					●	●				-		B	C
1436	複合影響	Scialli, Anthony R; Iannucci, Annette; Turim, Jay	Combining perfluoroalkane acid exposure levels for risk assessment	2007	Regul Toxicol Pharmacol. 2007 Dec;49(3):195-202. doi: 10.1016/j.yrtph.2007.08.003. Epub 2007 Aug 24.	Perfluoroalkane acids are present in biologic samples from >90% of people in the developed world. Because people may be exposed to multiple perfluoroalkane acids, it is reasonable to consider whether the exposure levels of these agents can be combined for risk assessment purposes. To investigate this possibility, we considered whether the literature on perfluoroalkane acids could be used to justify a scaling system analogous to the Toxic Equivalency Factor (TEF) system used for polychlorinated biphenyls, polychlorinated dibenzo-p-dioxins, and polychlorinated dibenzofurans. We evaluated pairs of studies performed with different perfluoroalkane acids in the same species using the same design and found that endpoints for perfluorooctanesulfonate (PFOS), perfluorooctanoic acid (PFOA), perfluorobutanesulfonate (PFBS), and perfluorodecanoic acid (PFDA) could be discordant. We evaluated pairs of rat studies of PFOS, PFOA, and PFBS performed with the same design for which dose-response curves could be modeled for the concordant endpoints, but we were unable to identify a scaling system that gave values consistently within an order of magnitude for the same compounds. Currently available data do not support the combining of exposure levels of perfluoroalkane acids for risk assessment, although re-evaluation after additional data are available is recommended.					●	●				-		B	B
1437	相加性	Tatum, K.R., Das, K., Abbott, B.D. and Lau, C.	Developmental toxicity of perfluoroalkyl acid mixtures in CD-1 mice	2010	U.S. Environmental Protection Agency, Presented at Society of Toxicology, Salt Lake City, Utah, March 07-11.	Perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS) and perfluorononanoic acid (PFNA) belong to a family of fluoro-organic compounds known as perfluoroalkyl acids (PFAAs). PFAAs have been widely used in industrial and commercial applications, and have been found to be both ubiquitous and highly persistent in the environment. Previous studies have indicated robust developmental toxicity associated with exposure to PFOS, PFOA, and PFNA individually in laboratory rodent models. However, multiple PFAAs are present in the environment and detectable to varying extent in humans. Hence, effects of these chemicals in mixtures must be taken into consideration for their health risk assessment. The current study examines the developmental effects of various mixtures of PFAAs and makes comparisons to exposures to individual compounds. Timed-pregnant CD-I mice were given PFAAs either alone (8 mg PFOA/kg, 12 mg PFOS/kg, 4 mg PFNA/kg) or in mixtures (4 mg PFOA/kg + 2 mg PFNA/kg; 4 mg PFOA/kg + 6 mg PFOS/kg; or 6 mg PFOS/kg + 2 mg PFNA/kg) by oral gavage daily from gestation day 1-17; controls received 0.5 % Tween vehicle. PFOS, PFOA and PFNA singly produced developmental effects as previously reported. In mixtures, PFAAs appeared to have a dose additive effect on maternal weight gain, pup body weight, as well as maternal and neonatal liver weights. In contrast, PFAAs in mixtures induced a less-than-dose additive effect on neonatal mortality. In particular, the PFOS + PFOA group responded less than PFOS or PFOA alone, where as PFOS + PFNA had no response at all. These data suggest that prenatal exposure to a mixture scheme of PFAAs with higher carbon-chain length (C-8 and C-9) containing either a carboxylic or sulfonic functional group produce additive effects on some endpoints and less-than-additive effects on neonatal mortality in CD-I mice. This abstract does not necessarily reflect U.S. EPA policy.					●	●				-		B	B
1438	複合影響	Abdellatif, A G; Préat, V; Vamecq, J; Nilsson, R; Roberfroid, M	Peroxisome proliferation and modulation of rat liver carcinogenesis by 2,4-dichlorophenoxyacetic acid, 2,4,5-trichlorophenoxyacetic acid, perfluorooctanoic acid and nafenopin	1990	Carcinogenesis. 1990 Nov;11(11):1899-902. doi: 10.1093/carcin/11.11.1899.	Using an initiation--selection--promotion protocol for induction of liver tumors in Wistar rats, the modulating action of various peroxisome proliferators on neoplasia as well as on selected biochemical parameters was studied. After treatment with diethylnitrosamine (DEN), the animals were subsequently subjected to a selection procedure involving feeding of 2-acetylaminofluorene (2-AAF), and in the middle of the 2-AAF treatment, a single necrogenic dose of carbon tetrachloride. Following a recovery period, the rats were fed a diet containing 0.1% nafenopin (NAF), 0.015% perfluorooctanoic acid (PFOA), 0.05% 2,4-dichlorophenoxyacetic acid (2,4-D), 0.05% 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) or 0.05% phenobarbital (PB) as a positive control. When the animals were killed, 7 months after initiation, the incidence of hepatocellular carcinoma was 83, 33 and 16% in the animals treated with NAF, PFOA or 2,4,5-T respectively. No cancers were observed in controls, or in the 2,4,-D groups. In comparison with controls, NAF and PFOA caused a 60-and 24-fold increase inthe peroxisomal beta-oxidation of fatty acids respectively, but only about a 2-fold increase in the catalase activity, 2,4-D and/or 2,4,5-T were much less active in this respect, giving approximately a doubling in the rate of fatty acid oxidation. The specific activity of D-amino acid and glycolate oxidases were significantly depressed, whereas the urate oxidase levels were apparently unaffected by the NAF and PFOA treatment. The results suggest that the selective induction of peroxisomal fatty acid oxidation is consistent with the hypothesis that imbalance between H2O2 overproduction and its destruction could play a role in the modulation of hepatocarcinogenesis by peroxisome proliferators.						●				-		D	B
1439	相加性	Bonefeld-Jorgensen, E., Long, M., Bossi, R., Ayotte, P., Asmund, G., Kruger, T., et al.	Cumulative risk assessment: principles and concepts	2009	Assessment of combined exposures to multiple chemicals: Report of a WHO/IPCS international workshop on aggregate/cumulative risk assessment. pp. 38–41. Available at: www.who.int/ipcs/methods/harmonization/areas/workshopreportdocument7.pdf	No abstract available						●				WHOガイダンス		D	D
1440	実験動物（反復投与毒性）	Goldenthal, E. I.; Jessup, D. C.; Geil, R. G.; Jefferson, N. D.; Arceo, R. J.	Ninety-day subacute rat toxicity study on Fluorad® Fluorochemical FC-143, International Research and Development Corporation, Study No. 137-089/090	1978	U.S. Environmental Protection Agency Administrative Record 226-0441/0447	No abstract available						●				Administrative Record 226-0441/0447で検索したが入手不可		D	D

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献ランク①	文献ランク②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1441	実験動物（肝毒性）	Metrick, M. and Marias, A.J.	28-day oral toxicity study with fc-143 in albino rats, Final Report, Industrial Bio-Test Laboratories, Inc. Study No. 8532-10654	1977	3M Reference No. T-1742CoC, Lot 269, September 29. [cited in OECD (2008)].	No abstract available						●				企業データ		D	D
1442	相加性	Peter, J.M and Gonzalez, F.J.	Why toxic equivalence factors are not suitable for perfluoroalkyl chemicals	2011	Chem. Res. Toxicol., 24: 1601–1609. doi: 10.1021/tx200316x	The pervasive nature of perfluoroalkyl chemicals in the environment has generated considerable interest for developing new strategies for risk assessment. In experimental animal models, exposure to perfluoroalkyl chemicals can cause developmental toxicity and hepatotoxicity. Peroxisome proliferator-activated receptor-α (PPARα) is required to mediate some but not all of these effects. Since PPARα has a role in mediating some of these effects, and there is some overlap in the type of toxicities elicited by perfluoroalkyl chemicals, it has been suggested that a scaling system analogous to the toxic equivalency factor (TEF) system used for polychlorinated dibenzo-p-dioxins (PCDD), polychlorinated dibenzofurans (PCDF), and polychlorinated biphenyls (PCB) could be used for perfluoroalkyl chemicals. However, evidence suggests that perfluoroalkyl chemicals can activate/interfere with other receptors, and there is reason to suggest the possibility of species differences in the response mediated by different receptors as well as qualitative differences in toxicities elicited by perfluoroalkyl chemicals. These differences and other data gaps preclude the development of a TEF approach for perfluoroalkyl chemicals.						●				-		D	B
1443	実験動物（肝毒性）	Qazi, M.R., Abedi, M.R., Nelson, B.D., DePierre, J.W. and Abedi-Valugerdi, M.	Dietary exposure to perfluorooctanoate or perfluorooctane sulfonate induces hypertrophy in centrilobular hepatocytes and alters the hepatic immune status in mice	2010	Int. Immunopharmacol., 10(11): 1420–1427. doi: 10.1016/j.intimp.2010.08.009. Epub 2010 Sep 1.	It is well established that exposure of mice to perfluorooctanoate (PFOA) or perfluorooctane sulfonate (PFOS) induces hepatomegaly and, concurrently, immunotoxicity. However, the effects of these perfluorochemicals on the histology and immune status of the liver have not been yet investigated and we have examined these issues here. Dietary treatment of male C57BL/6 mice with 0.002% (w/w) PFOA or 0.005% (w/w) PFOS for 10 days resulted in significant reductions in serum levels of cholesterol and triglycerides, a moderate increase in the serum activity of alkaline phosphatase (ALP) and hepatomegaly, without affecting other immune organs. This hepatomegaly was associated with marked hypertrophy of the centrilobular hepatocytes, with elevated numbers of cytoplasmic acidophilic granules and occasional mitosis. Furthermore, dietary exposure to PFOA or PFOS altered the hepatic immune status: whereas exposure to PFOA enhanced the numbers of total, as well as of phenotypically distinct subpopulations of intrahepatic immune cells (IHIC), and in particular the presumptive erythrocyte progenitor cells, treatment with PFOS enhanced only the numbers of hepatic cells that appear immunophenotypically to be erythrocyte progenitors, without affecting other types of IHIC. In addition, exposure to these compounds attenuated hepatic levels of tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ) and interleukin-4 (IL-4). Furthermore, the exposed animals exhibited a significant increase in hepatic levels of erythropoietin, a hormone required for erythropoiesis. Thus, in mice, PFOA- and PFOS-induced hepatomegaly is associated with significant alterations in hepatic histophysiology and immune status, as well as induction of hepatic erythropoiesis.						●				-		B	B
1444	相加性	Wei, Yanhong; Shi, Xiongjie; Zhang, Hongxia; Wang, Jianshe; Zhou, Bingsheng; Dai, Jiayin	Combined effects of polyfluorinated and perfluorinated compounds on primary cultured hepatocytes from rare minnow (Gobiocypris rarus) using toxicogenomic analysis	2009	Aquat Toxicol. 2009 Oct 19;95(1):27-36. doi: 10.1016/j.aquatox.2009.07.020. Epub 2009 Aug 5.	Polyfluorinated and perfluorinated compounds (PFCs) are used in numerous commercial products and have been ubiquitously detected in the environment as well as in the blood of humans and wildlife. To assess the combined effects caused by PFCs in mixtures, gene expression profiles were generated using a custom cDNA microarray to detect changes in primary cultured hepatocytes of rare minnows exposed to six individual PFCs (perfluorooctanoic acid, perfluorononanoic acid, perfluorododecanoic acid, perfluorododecanoic acid, perfluorooctane sulfonate, and 8:2 fluorotelomer alcohol) and four formulations of the PFCs mixtures. Mixtures as well as individual compounds consistently regulated a particular gene set, which suggests that these conserved genes may play a central role in the toxicity mediated by PFCs. Specifically, a number of genes regulated by the mixtures were identified in this study, which were not affected by exposure to any single component. These genes are implicated in multiple biological functions and processes, including fatty acid metabolism and transport, xenobiotic metabolism, immune responses, and oxidative stress. More than 80% of the altered genes in the PFOA- and PFOS-dominant mixture groups were of the same gene set, while the gene expression profiles from single PFOA and PFOS exposures were not as similar. This work contributes to the development of toxicogenomic approaches in combined toxicity assessment and allows for comprehensive insights into the combined action of PFCs mixtures in multiple environmental matrices.						●				-		C	
1445	相加性	WHO	Chemical mixtures in source water and drinking-water	2017	World Health Organization, Geneva, Switzerland. https://www.who.int/publications/i/item/9789241512374	No abstract available						●				WHOガイダンス		D	D
1446	相加性	Wilson, Jodie; Berntsen, Hanne Friis; Zimmer, Karin Elisabeth; Verhaegen, Steven; Frizzell, Caroline; Ropstad, Erik; Connolly, Lisa	Do persistent organic pollutants interact with stress response? Individual compounds, and their mixtures, interaction with the glucocorticoid receptor	2016	Toxicol Lett. 2016 Jan 22;241:121-32. doi: 10.1016/j.toxlet.2015.11.014. Epub 2015 Nov 17.	Persistent organic pollutants (POPs) are toxic substances, highly resistant to environmental degradation, which can bio-accumulate and have long-range atmospheric transport potential (UNEP, 2001). The majority of studies on endocrine disruption have focused on interferences on the sexual steroid hormones and so have overlooked disruption to glucocorticoid hormones. Here the endocrine disrupting potential of individual POPs and their mixtures has been investigated in vitro to identify any disruption to glucocorticoid nuclear receptor transcriptional activity. POP mixtures were screened for glucocorticoid receptor (GR) translocation using a GR redistribution assay (RA) on a CellInsight™ NXT high content screening (HCS) platform. A mammalian reporter gene assay (RGA) was then used to assess the individual POPs, and their mixtures, for effects on glucocorticoid nuclear receptor transactivation. POP mixtures did not induce GR translocation in the GR RA or produce an agonist response in the GR RGA. However, in the antagonist test, in the presence of cortisol, an individual POP, p,p'-dichlorodiphenyldichloroethylene (p,p'-DDE), was found to decrease glucocorticoid nuclear receptor transcriptional activity to 72.5% (in comparison to the positive cortisol control). Enhanced nuclear transcriptional activity, in the presence of cortisol, was evident for the two lowest concentrations of perfluorodecanoic acid (PFOS) potassium salt (0.0147mg/ml and 0.0294mg/ml), the two highest concentrations of perfluorodecanoic acid (PFDA) (0.0025mg/ml and 0.005mg/ml) and the highest concentration of 2,2',4,4'-tetrabromodiphenyl ether (BDE-47) (0.0000858mg/ml). It is important to gain a better understanding of how POPs can interact with GRs as the disruption of glucocorticoid action is thought to contribute to complex diseases.						●				-		D	B
1447	MOA（肝毒性）	Dong, Hongyan; Curran, Ivan; Williams, Andrew; Bondy, Genevieve; Yauk, Carole L; Wade, Michael G	Hepatic miRNA profiles and thyroid hormone homeostasis in rats exposed to dietary potassium perfluorooctanesulfonate (PFOS)	2016	Environ Toxicol Pharmacol. 2016 Jan;41:201-10. doi: 10.1016/j.etap.2015.12.009. Epub 2015 Dec 21.	Perfluorooctanesulfonate (PFOS) has been widely used in a variety of industrial and commercial applications as a surfactant and stain repellent. PFOS causes liver damage (including liver tumors) in experimental animals, primarily via interaction with PPARα and CAR/PXR. We investigated the involvement of microRNAs (miRNAs) in PFOS-induced hepatotoxicity, and mechanisms involved in abnormal thyroid hormone (TH) homeostasis, in the livers of adult male rats exposed in feed to 50mg PFOS/kg diet for 28 days. PFOS-treated rats exhibited expected histopathological and clinical chemistry changes, and global gene expression changes consistent with the involvement of PPARα and CAR/PXR. Thirty-eight miRNAs were significantly altered. Three members of the miR-200 family were the most increased, while miR-122-5p and miR-21-5p were the most decreased, in PFOS-treated rats. Expression of the miR-23b-3p/27b-3p/24-3p cluster also decreased in PFOS-treated animals. Pathway analysis of miRNAs and associated gene expression changes suggests involvement of epithelial to mesenchymal transition (EMT), which is a primary process of tumor cell motility and cancer metastasis. Our analysis also revealed transcripts that may mediate PFOS-induced effects on TH homeostasis including: activation of the CAR/PXR pathway, phase II/III enzymes, and deiodinase. These changes are consistent with low serum TH due to enhanced metabolic clearance of TH. However, most TH hepatic target genes were not altered in a manner consistent with reduced TH signaling, suggesting that PFOS exposure did not induce functional hypothyroidism. Collectively, the study suggests an important role for miRNAs in PFOS-induced hepatotoxicity and provides insight into the effects of PFOS on TH homeostasis.							●			-		B	B
1448	MOA（肝毒性）	Holsapple, Michael P; Pitot, Henri C; Cohen, Samuel M; Boobis, Alan R; Klaunig, James E; Pastoor, Timothy; Dellarco, Vicki L; Dragan, Yvonne P	Mode of action in relevance of rodent liver tumors to human cancer risk	2006	Toxicol Sci. 2006 Jan;89(1):51-6. doi: 10.1093/toxsci/kfj001. Epub 2005 Oct 12.	Hazard identification and risk assessment paradigms depend on the presumption of the similarity of rodents to humans, yet species specific responses, and the extrapolation of high-dose effects to low-dose exposures can affect the estimation of human risk from rodent data. As a consequence, a human relevance framework concept was developed by the International Programme on Chemical Safety (IPCS) and International Life Sciences Institute (ILSI) Risk Science Institute (RSI) with the central tenet being the identification of a mode of action (MOA). To perform a MOA analysis, the key biochemical, cellular, and molecular events need to first be established, and the temporal and dose-dependent concordance of each of the key events in the MOA can then be determined. The key events can be used to bridge species and dose for a given MOA. The next step in the MOA analysis is the assessment of biological plausibility for determining the relevance of the specified MOA in an animal model for human cancer risk based on kinetic and dynamic parameters. Using the framework approach, a MOA in animals could not be defined for metal overload. The MOA for phenobarbital (PB)-like P450 inducers was determined to be unlikely in humans after kinetic and dynamic factors were considered. In contrast, after these factors were considered with reference to estrogen, the conclusion was drawn that estrogen-induced tumors were plausible in humans. Finally, it was concluded that the induction of rodent liver tumors by porphyrogenic compounds followed a cytotoxic MOA, and that liver tumors formed as a result of sustained cytotoxicity and regenerative proliferation are considered relevant for evaluating human cancer risk if appropriate metabolism occurs in the animal models and in humans.							●			-		C	C
1449	MOA（PPAR）	Yu, Xiao-Hua; Zheng, Xi-Long; Tang, Chao-Ke	Peroxisome Proliferator-Activated Receptor α in Lipid Metabolism and Atherosclerosis	2015	Adv Clin Chem. 2015;71:171-203. doi: 10.1016/bs.acc.2015.06.005. Epub 2015 Jul 23.	Atherosclerosis is a chronic inflammatory disease with deposition of excessive cholesterol in the arterial intima. Peroxisome proliferator-activated receptor α (PPARα) is a nuclear receptor that can activate or inhibit the expression of many target genes by forming a heterodimer complex with the retinoid X receptor. Activation of PPARα plays an important role in the metabolism of multiple lipids, including high-density lipoprotein, cholesterol, low-density lipoprotein, triglyceride, phospholipid, bile acids, and fatty acids. Increased PPARα activity also mitigates atherosclerosis by blocking macrophage foam cell formation, vascular inflammation, vascular smooth muscle cell proliferation and migration, plaque instability, and thrombogenicity. Clinical use of synthetic PPARα agonist fibrate improved dyslipidemia and attenuated atherosclerosis-related disease risk. This review summarizes PPARα in lipid and lipoprotein metabolism and atherosclerosis, and also highlights its potential therapeutic benefits.							●			-		C	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	情報抽出	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022					
1450	実験動物（代謝）	Curran, I.; Hierlihy, S. L.; Liston, V.; Pantazopoulos, P.; Nunnikhoven, A.; Tittlemier, S.; Barker, M.; Trick, K.; Bondy, G.	Altered fatty acid homeostasis and related toxicologic sequelae in rats exposed to dietary potassium perfluorooctanesulfonate (PFOS)	2008	J Toxicol Environ Health A. 71: 1526-1541. doi: 10.1080/15287390802361763.	Perfluorooctanesulfonate (PFOS) is one of a class of industrial chemicals known as perfluoroalkyl acids, which have a wide variety of uses as surfactants and stain repellants. The presence of fluorochemical residues in human blood, plasma, or serum from sample populations worldwide is indicative of widespread human exposure. Previous studies demonstrated that PFOS alters fatty acid metabolism in the liver of rodents and that this leads to peroxisome proliferation. This study was undertaken to -1 confirm the effects of PFOS on rat liver, -2 identify additional target organs and systems, and -3 further explore the biochemical and molecular changes associated with PFOS exposure. The results confirmed that liver was a primary target for PFOS. Hepatomegaly, decreased serum triglycerides and cholesterol, and increased expression of the genes for acyl-coenzymeA oxidase 1 (ACOX1) and cytochrome P-450 4A22 (CYP4A22) were indicative of exposure to a peroxisome proliferator. Changes in liver fatty acid profiles included increased total monounsaturated fatty acid levels and decreased total polyunsaturated fatty acids, as well as an increase in linoleic acid levels and a decrease in longer chain fatty acids. These changes were similar to those induced by relatively weak peroxisome proliferators. Disruptions in hepatic fatty acid metabolism may contribute to changes in red blood cell membranes, resulting in increased lysis and cell fragility. Serum thyroid hormone levels were decreased in PFOS-treated rats, while the kidney and cardiovascular systems were not significant targets. Residue analyses indicated that PFOS accumulation in tissues was dose dependent, appearing preferentially in the liver at lower doses but increasing in serum and other organs relative to liver at higher doses.	●	●		●			●		●	-			B	B
1451	実験動物（生殖発生毒性）	Lv, Z.; Li, G.; Li, Y.; Ying, C.; Chen, J.; Chen, T.; Wei, J.; Lin, Y.; Jiang, Y.; Wang, Y.; Shu, B.; Xu, B.; Xu, S.	Glucose and lipid homeostasis in adult rat is impaired by early-life exposure to perfluorooctane sulfonate	2014	Environ Toxicol. 2013 Sep;28(9):532-42. doi: 10.1002/tox.20747. Epub 2011 Aug 24.	Perfluorooctane sulfonate (PFOS), which belongs to the degradation product of many perfluorinated compounds, is on the list of persistent organic pollutants (POPs) and is currently detected in both wildlife and humans. The consequence of gestational and lactational exposure to PFOS on prediabetes effect in offspring was investigated in rats in the present study. Maternal rats were treated with vehicle, 0.5 mg/kg/day or 1.5 mg/kg/day PFOS respectively from gestation day 0 to postnatal day 21 The glucose and lipid metabolism effects were investigated on the offspring in adulthood. The gestational and lactational exposure to PFOS led to low body weight from birth to weaning, and evoked signs of a prediabetic state, with elevated fasting serum insulin and leptin level, impaired glucose tolerance, though the fasting serum glucose and glycosylated serum protein level were normal. Abnormal lipid homeostasis was also observed by the phenomenon of hepatic steatosis and increased gonadal fat pad weight. However, the circulating serum level of fasting triglyceride and cholesterol level were no different from controls. Our results suggested that developmental exposure to PFOS may contribute to glucose and lipid metabolic disorder in adulthood.	●	●		●						-		1	B	A
1452	実験動物（代謝）	Pouwer, Marianne G; Pieterman, Elsbet J; Chang, Shu-Ching; Olsen, Geary W; Caspers, Martien P M; Verschuren, Lars; Jukema, J Wouter; Princen, Hans M G	Dose effects of ammonium perfluorooctanoate on lipoprotein metabolism in apoe*3-leiden	2009	Toxicol Sci. 2019 Apr 1;168(2):519-534. doi: 10.1093/toxsci/kfz015.	Epidemiological studies have reported positive associations between serum perfluorooctanoic acid (PFOA) and total and non-high-density lipoprotein cholesterol (non-HDL-C) although the magnitude of effect of PFOA on cholesterol lacks consistency. The objectives of this study were to evaluate the effect of PFOA on plasma cholesterol and triglyceride metabolism at various plasma PFOA concentrations relevant to humans, and to elucidate the mechanisms using APOE*3-Leiden.CETP mice, a model with a human-like lipoprotein metabolism. APOE*3-Leiden.CETP mice were fed a Western-type diet with PFOA (10, 300, 30 000 ng/g/d) for 4-6 weeks. PFOA exposure did not alter plasma lipids in the 10 and 300 ng/g/d dietary PFOA dose groups. At 30 000 ng/g/d, PFOA decreased plasma triglycerides (TG), total cholesterol (TC), and non-HDL-C, whereas HDL-C was increased. The plasma lipid alterations could be explained by decreased very low-density lipoprotein (VLDL) production and increased VLDL clearance by the liver through increased lipoprotein lipase activity. The concomitant increase in HDL-C was mediated by decreased cholesteryl ester transfer activity and changes in gene expression of proteins involved in HDL metabolism. Hepatic gene expression and pathway analysis confirmed the changes in lipoprotein metabolism that were mediated for a major part through activation of the peroxisome proliferator-activated receptor (PPAR)α. Our data confirmed the findings from a phase 1 clinical trial in humans that demonstrated high serum or plasma PFOA levels resulted in lower cholesterol levels. The study findings do not show an increase in cholesterol at environmental or occupational levels of PFOA exposure, thereby indicating these findings are associative rather than causal.	●	●								-			B	B
1453	実験動物（神経毒性）	Salgado, R.; López-Doval, S.; Pereiro, N.; Lafuente, A.	Perfluorooctane sulfonate (PFOS) exposure could modify the dopaminergic system in several limbic brain regions	2008	Toxicol Lett. 2016 Jan 5;240(1):226-35. doi: 10.1016/j.toxlet.2015.10.023. Epub 2015 Oct 31.	Perfluorooctane sulfonate (PFOS) is the most representative of a rising class of persistent organic pollutants perfluorochemicals. In the present study, its neurotoxicity was examined using adult male rats orally treated with 0.5; 1.0; 3 and 6 mg of PFOS/kg/day for 28 days. At the end of the treatment, the dopamine concentration and its metabolism expressed like the ratio 3,4-dihydroxyphenylacetic acid (DOPAC)/dopamine and homovanillic acid (HVA)/dopamine were measured in the amygdala, prefrontal cortex and hippocampus. Gene and protein expression of the dopamine receptors D1 and D2 were also determined in these limbic areas. The obtained results suggest that: -1 PFOS can alter the dopamine system by modifying its neuronal activity and/or its D1 and D2 receptors in the studied brain regions; -2 the dopamine concentration and metabolism seem to be more sensitive against PFOS toxicity in the hippocampus than in the other analyzed brain areas; -3 the inhibited gene and protein expression of the D1 receptors induced by PFOS in the amygdala could be related to several changes in the HPA axis activity, and lastly; -4 the observed alterations on the dopamine system induced by PFOS could be a possible neurotoxicity mechanism of PFOS, leading to many neurological diseases.	●	●								-		1	B	A
1454	実験動物（代謝）	Wang, L.; Wang, Y.; Liang, Y.; Li, J.; Liu, Y.; Zhang, J.; Zhang, A.; Fu, J.; Jiang, G.	PFOS induced lipid metabolism disturbances in BALB/c mice through inhibition of low density lipoproteins excretion	2014	Sci Rep. 4: 4582. doi: 10.1038/srep04582.	Male BALB/c mice fed with either a regular or high fat diet were exposed to 0, 5 or 20 mg/kg perfluorooctane sulfonate (PFOS) for 14 days. Increased body weight, serum glucose, cholesterol and lipoprotein levels were observed in mice given a high fat diet. However, all PFOS-treated mice got reduced levels of serum lipid and lipoprotein. Decreasing liver glycogen content was also observed, accompanied by reduced serum glucose levels. Histological and ultrastructural examination detected more lipid droplets accumulated in hepatocytes after PFOS exposure. Moreover, transcripitonal activity of lipid metabolism related genes suggests that PFOS toxicity is probably unrelevant to PPARα's transcription. The present study demonstrates a lipid disturbance caused by PFOS and thus point to its role in inhibiting the secretion and normal function of low density lipoproteins.	●	●					●		●	-			B	B
1455	実験動物（代謝）	Yu, Nanyang; Wei, Si; Li, Meiying; Yang, Jingping; Li, Kan; Jin, Ling; Xie, Yuwei; Giesy, John P; Zhang, Xiaowei; Yu, Hongxia	Effects of Perfluorooctanoic Acid on Metabolic Profiles in Brain and Liver of Mouse Revealed by a High-throughput Targeted Metabolomics Approach	2016	Sci Rep. 2016 Apr 1;6:23963. doi: 10.1038/srep23963.	Perfluorooctanoic acid (PFOA), a perfluoroalkyl acid, can result in hepatotoxicity and neurobehavioral effects in animals. The metabolome, which serves as a connection among transcriptome, proteome and toxic effects, provides pathway-based insights into effects of PFOA. Since understanding of changes in the metabolic profile during hepatotoxicity and neurotoxicity were still incomplete, a high-throughput targeted metabolomics approach (278 metabolites) was used to investigate effects of exposure to PFOA for 28 d on brain and liver of male Balb/c mice. Results of multivariate statistical analysis indicated that PFOA caused alterations in metabolic pathways in exposed individuals. Pathway analysis suggested that PFOA affected metabolism of amino acids, lipids, carbohydrates and energetics. Ten and 18 metabolites were identified as potential unique biomarkers of exposure to PFOA in brain and liver, respectively. In brain, PFOA affected concentrations of neurotransmitters, including serotonin, dopamine, norepinephrine, and glutamate in brain, which provides novel insights into mechanisms of PFOA-induced neurobehavioral effects. In liver, profiles of lipids revealed involvement of β-oxidation and biosynthesis of saturated and unsaturated fatty acids in PFOA-induced hepatotoxicity, while alterations in metabolism of arachidonic acid suggesting potential of PFOA to cause inflammation response in liver. These results provide insight into the mechanism and biomarkers for PFOA-induced effects.	●	●								-			B	B
1456	in vitro（代謝）	Nabb, Diane L; Szostek, Bogdan; Himmelstein, Matthew W; Mawn, Michael P; Gargas, Michael L; Sweeney, Lisa M; Stadler, Judith C; Buck, Robert C; Fasano, William J	In vitro metabolism of 8-2 fluorotelomer alcohol: interspecies comparisons and metabolic pathway refinement	2007	Toxicol Sci. 2007 Dec;100(2):333-44. doi: 10.1093/toxsci/kfm230. Epub 2007 Sep 4.	The detection of perfluorinated organic compounds in the environment has generated interest in their biological fate. 8-2 Fluorotelomer alcohol (8-2 FTOH, C(7)F(15)CF(2)CH(2)CH(2)OH), a raw material used in the manufacture of fluorotelomer-based products, has been identified in the environment and has been implicated as a potential source for perfluorooctanoic acid (PFOA) in the environment. In this study, the in vitro metabolism of [3-(14)C] 8-2 FTOH and selected acid metabolites by rat, mouse, trout, and human hepatocytes and by rat, mouse, and human liver microsomes and cytosol were investigated. Clearance rates of 8-2 FTOH in hepatocytes indicated rat > mouse > human >/= trout. A number of metabolites not previously reported were identified, adding further understanding to the pathway for 8-2 FTOH metabolism. Neither perfluorooctanoate nor perfluorononanoate was detected from incubations with human microsomes. To further elucidate the steps in the metabolic pathway, hepatocytes were incubated with 8-2 fluorotelomer acid, 8-2 fluorotelomer unsaturated acid, 7-3 acid, 7-3 unsaturated acid, and 7-2 secondary fluorotelomer alcohol. Shorter chain perfluorinated acids were only observed in hepatocyte and microsome incubations of the 8-2 acids but not from the 7-3 acids. Overall, the results indicate that 8-2 FTOH is extensively metabolized in rats and mice and to a lesser extent in humans and trout. Metabolism of 8-2 FTOH to perfluorinated acids was extremely small and likely mediated by enzymes in the microsomal fraction. These results suggest that human exposure to 8-2 FTOH is not expected to be a significant source of PFOA or any other perfluorocarboxylic acids.			●	●						-			B	C
1457	実験動物（代謝）	Haughom, B; Spydevold, O	The mechanism underlying the hypolipemic effect of perfluorooctanoic acid (PFOA), perfluorooctane sulphonic acid (PFOSA) and clofibric acid	1992	Biochim Biophys Acta. 1992 Sep 22;1128(1):65-72. doi: 10.1016/0005-2760(92)90258-w.	The influence of the peroxisomal proliferators perfluorooctanoic acid (PFOA), perfluorooctane sulphonic acid (PFOSA) and clofibric acid on lipid metabolism in rats was studied. Dietary treatment of male Wistar rats with these three compounds resulted in rapid and pronounced reduction in both cholesterol and triacylglycerols in serum. The concentration of liver triacylglycerols was increased by about 300% by PFOSA. Free cholesterol was increased by both perfluoro compounds. Cholesteryl ester was reduced to 50% by PFOSA as well by clofibrate. In hepatocytes from fed rats, all the compounds resulted in reduced cholesterol synthesis from acetate, pyruvate and hydroxymethyl glutarate, but there was no reduction of synthesis from mevalonic acid. The oxidation of palmitate was also increased in all groups. The perfluoro compounds, but not clofibrate, caused some reduction in fatty acid synthesis. The activity of liver HMG-CoA reductase was reduced to 50% or less in all treatment groups and all three compounds led to lower activity of acyl-CoA:cholesterol acyltransferase (ACAT). Changes in other enzymes related to lipid metabolism were inconsistent. The present data suggest that the hypolipemic effect of these compounds may, at least partly, be mediated via a common mechanism; impaired production of lipoprotein particles due to reduced synthesis and esterification of cholesterol together with enhanced oxidation of fatty acids in the liver.				●						-			B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献ランク①	文献ランク②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1458	実験動物（代謝）	Permadi, H; Lundgren, B; Andersson, K; DePierre, J W	Effects of perfluoro fatty acids on xenobiotic-metabolizing enzymes, enzymes which detoxify reactive forms of oxygen and lipid peroxidation in mouse liver	1992	Biochem Pharmacol. 1992 Sep 25;44(6):1183-91. doi: 10.1016/0006-2952(92)90383-t.	Male mice were exposed via their diet to perfluoro fatty acids of various chain-lengths (2-10 carbon atoms) at different doses (0.02 and 0.1% weight) and for different periods of time (2-10 days). Thereafter, we monitored effects on liver and body weights and a number of hepatic parameters, including mitochondrial protein content, microsomal contents of cytochromes P450 and b5, NADPH-cytochrome P450 reductase activity [measured as NADPH-cytochrome c reductase (EC 1.6.2.3)], microsomal and cytosolic epoxide hydrolase (EC 3.3.2.3) activities, cytosolic DT-diaphorase (EC 1.6.99.2), glutathione transferase (EC 2.5.1.18), glutathione peroxidase (EC 1.11.1.9) and superoxide dismutase (EC 1.15.1.1) activities, and levels of thiobarbituric acid-reactive material (as an indicator of lipid peroxidation) in the mitochondrial subfraction. The most dramatic changes observed were a 5-9-fold increase in mitochondrial protein, a 3-6-fold increase in the microsomal content of cytochrome P450, a 3-10-fold increase in cytosolic DT-diaphorase activity, an approximately 2-fold increase in cytosolic epoxide hydrolase activity and as much as a 60% decrease in the level of thiobarbituric acid-reactive compounds in the mitochondrial fraction. Smaller increases in microsomal epoxide hydrolase activity and decreases in cytosolic glutathione peroxidase activity were also observed. Of the perfluoro fatty acids tested, perfluorooctanoic acid caused the largest changes in the parameters examined here. Dietary exposure of mice to a 0.02% dose of this substance for 10 days results in a maximal or near-maximal effect in most cases.				●						-		B	B
1459	実験動物（肝毒性）	Permadi, H; Lundgren, B; Andersson, K; Sundberg, C; DePierre, J W	Effects of perfluoro fatty acids on peroxisome proliferation and mitochondrial size in mouse liver: Dose and time factors and effect of chain length	1993	Xenobiotica. 1993 Jul;23(7):761-70. doi: 10.3109/00498259309166782.	1. Male mice were fed a diet containing perfluoro fatty acids of varying chain length (i.e. perfluoroacetic, -butyric, -octanoic and -decanoic acids) at different doses (0.02 or 0.1% w/w of diet) for different periods of time (2-10 days), and effects on liver weight, hepatic mitochondrial protein and hepatic peroxisomal palmitoyl-CoA oxidation, lauroyl-CoA oxidase and catalase were monitored. 2. The greatest effects were obtained with perfluoro-octanoic and perfluoro decanoic acids, while perfluoro acetic acid was inactive. The effects with 0.02% w/w of diet perfluoro-octanoic acid were at least as great as those observed with 0.1%. A more detailed dose-response investigation focused on perfluoro-octanoic acid revealed that maximal effects with this substance could be obtained with a dietary dose of 0.01% for 10 days and that significant changes were also observed with 0.001%. 3. Maximal effects with 0.02% w/w of diet perfluoro-octanoic acid were attained after 6-10 days of feeding. 4. As with other peroxisome proliferators, perfluoro fatty acids increase mouse hepatic peroxisomal fatty acid beta-oxidation more extensively than they increase catalase, thus increasing hepatic oxidative stress. 5. As with other peroxisome proliferators, perfluoro fatty acids increase mouse liver mitochondrial protein. This effect is due primarily to a redistribution of mitochondria from the nuclear to the mitochondrial fraction, caused by an apparent decrease in the mean size of hepatic mitochondria after treatment.				●						-	1	B	A
1460	実験動物（代謝）	Rebholz, Sandra L; Jones, Thomas; Herrick, Robert L; Xie, Changchun; Calafat, Antonia M; Pinney, Susan M; Woollett, Laura A	Hypercholesterolemia with consumption of PFOA-laced Western diets is dependent on strain and sex of mice	2016	Toxicol Rep. 2016;3:46-54. doi: 10.1016/j.toxrep.2015.11.004.	Perfluorooctanoic acid (PFOA) is a man-made surfactant with a number of industrial applications. It has a long half-life environmentally and biologically. Past studies suggest a direct relationship between plasma cholesterol and PFOA serum concentrations in humans and an inverse one in rodents fed standard rodent chow, making it difficult to examine mechanisms responsible for the potential PFOA-induced hypercholesterolemia and altered sterol metabolism. To examine dietary modification of PFOA-induced effects, C57BL/6 and BALB/c mice were fed PFOA in a fat- and cholesterol-containing diet. When fed these high fat diets, PFOA ingestion resulted in marked hypercholesterolemia in male and female C57BL/6 mice and less robust hypercholesterolemia in male BALB/c mice. The PFOA-induced hypercholesterolemia appeared to be the result of increased liver masses and altered expression of genes associated with hepatic sterol output, specifically bile acid production. mRNA levels of genes associated with sterol input were reduced only in C57BL/6 females, the mice with the greatest increase in plasma cholesterol levels. Strain-specific PFOA-induced changes in cholesterol concentrations in mammary tissues and ovaries paralleled changes in plasma cholesterol levels. mRNA levels of sterol-related genes were reduced in ovaries of C57BL/6 but not in BALB/c mice and not in mammary tissues. Our data suggest that PFOA ingestion leads to hypercholesterolemia in mice fed fat and cholesterol and effects are dependent upon the genetic background and gender of the mice with C57BL/6 female mice being most responsive to PFOA.				●		●				-		B	B
1461	実験動物（代謝）	Staels, B; Dallongeville, J; Auwerx, J; Schoonjans, K; Leitersdorf, E; Fruchart, J C	Mechanism of action of fibrates on lipid and lipoprotein metabolism	1998	Circulation. 1998 Nov 10;98(19):2088-93. doi: 10.1161/01.cir.98.19.2088.	Treatment with fibrates, a widely used class of lipid-modifying agents, results in a substantial decrease in plasma triglycerides and is usually associated with a moderate decrease in LDL cholesterol and an increase in HDL cholesterol concentrations. Recent investigations indicate that the effects of fibrates are mediated, at least in part, through alterations in transcription of genes encoding for proteins that control lipoprotein metabolism. Fibrates activate specific transcription factors belonging to the nuclear hormone receptor superfamily, termed peroxisome proliferator-activated receptors (PPARs). The PPAR-alpha form mediates fibrate action on HDL cholesterol levels via transcriptional induction of synthesis of the major HDL apolipoproteins, apoA-I and apoA-II. Fibrates lower hepatic apoC-III production and increase lipoprotein lipase--mediated lipolysis via PPAR. Fibrates stimulate cellular fatty acid uptake, conversion to acyl-CoA derivatives, and catabolism by the beta-oxidation pathways, which, combined with a reduction in fatty acid and triglyceride synthesis, results in a decrease in VLDL production. In summary, both enhanced catabolism of triglyceride-rich particles and reduced secretion of VLDL underlie the hypotriglyceridemic effect of fibrates, whereas their effect on HDL metabolism is associated with changes in HDL apolipoprotein expression.				●						-		D	C
1462	実験動物（代謝）	Tan, Xiaobing; Xie, Guoxiang; Sun, Xiuhua; Li, Qiong; Zhong, Wei; Qiao, Peter; Sun, Xinguo; Jia, Wei; Zhou, Zhanxiang	High fat diet feeding exaggerates perfluorooctanoic acid-induced liver injury in mice via modulating multiple metabolic pathways	2013	PLoS One. 2013 Apr 23;8(4):e61409. doi: 10.1371/journal.pone.0061409. Print 2013.	High fat diet (HFD) is closely linked to a variety of health issues including fatty liver. Exposure to perfluorooctanoic acid (PFOA), a synthetic perfluorinated carboxylic acid, also causes liver injury. The present study investigated the possible interactions between high fat diet and PFOA in induction of liver injury. Mice were pair-fed a high-fat diet (HFD) or low fat control with or without PFOA administration at 5 mg/kg/day for 3 weeks. Exposure to PFOA alone caused elevated plasma alanine aminotransferase (ALT) and alkaline phosphatase (ALP) levels and increased liver weight along with reduced body weight and adipose tissue mass. HFD alone did not cause liver damage, but exaggerated PFOA-induced hepatotoxicity as indicated by higher plasma ALT and AST levels, and more severe pathological changes including hepatocyte hypertrophy, lipid droplet accumulation and necrosis as well as inflammatory cell infiltration. These additive effects of HFD on PFOA-induced hepatotoxicity correlated with metabolic disturbance in liver and blood as well as up-regulation of hepatic proinflammatory cytokine genes. Metabolomic analysis demonstrated that both serum and hepatic metabolite profiles of PFOA, HFD, or HFD-PFOA group were clearly differentiated from that of controls. PFOA affected more hepatic metabolites than HFD, but HFD showed positive interaction with PFOA on fatty acid metabolites including long chain fatty acids and acylcarnitines. Taken together, dietary high fat potentiates PFOA-induced hepatic lipid accumulation, inflammation and necrotic cell death by disturbing hepatic metabolism and inducing inflammation. This study demonstrated, for the first time, that HFD increases the risk of PFOA in induction of hepatotoxicity.				●		●				-		B	B
1463	in vitro（代謝）	Xu, Jialin; Shimpi, Prajakta; Armstrong, Laura; Salter, Deanna; Slitt, Angela L	PFOS induces adipogenesis and glucose uptake in association with activation of Nrf2 signaling pathway	2016	Toxicol Appl Pharmacol. 2016 Jan 1;290:21-30. doi: 10.1016/j.taap.2015.11.002. Epub 2015 Nov 5.	PFOS is a chemical of nearly ubiquitous exposure in humans. Recent studies have associated PFOS exposure to adipose tissue-related effects. The present study was to determine whether PFOS alters the process of adipogenesis and regulates insulin-stimulated glucose uptake in mouse and human preadipocytes. In murine-derived 3T3-L1 preadipocytes, PFOS enhanced hormone-induced differentiation to adipocytes and adipogenic gene expression, increased insulin-stimulated glucose uptake at concentrations ranging from 10 to 100μM, and enhanced Glucose transporter type 4 and Insulin receptor substrate-1 expression. Nuclear factor (erythroid-derived 2)-like 2 (Nrf2), NAD(P)H dehydrogenase, quinone 1 and Glutamate-cysteine ligase, catalytic subunit were significantly induced in 3T3-L1 cells treated with PFOS, along with a robust induction of Antioxidant Response Element (ARE) reporter in mouse embryonic fibroblasts isolated from ARE-hPAP transgenic mice by PFOS treatment. Chromatin immunoprecipitation assays further illustrated that PFOS increased Nrf2 binding to ARE sites in mouse Nqo1 promoter, suggesting that PFOS activated Nrf2 signaling in murine-derived preadipocytes. Additionally, PFOS administration in mice (100μg/kg/day) induced adipogenic gene expression and activated Nrf2 signaling in epididymal white adipose tissue. Moreover, the treatment on human visceral preadipocytes illustrated that PFOS (5 and 50μM) promoted adipogenesis and increased cellular lipid accumulation. It was observed that PFOS increased Nrf2 binding to ARE sites in association with Nrf2 signaling activation, induction of Peroxisome proliferator-activated receptor γ and CCAAT/enhancer-binding protein α expression, and increased adipogenesis. This study points to a potential role of PFOS in dysregulation of adipose tissue expandability, and warrants further investigations on the adverse effects of persistent pollutants on human health.				●						-		B	A
1464	実験動物（反復投与毒性）	Goldenthal, E.I., Jessup, D.C., Geil, R.G. and Mehring, J.S.	Ninety-day subacute rhesus monkey toxicity study. Study No. 137-092.	1978	US EPA Public Docket AR226-0447	No abstract available					●		●			企業データ		D	D
1465	実験動物（心血管系）	Getz, G. S.; Reardon, C. A.	Animal models of atherosclerosis [Review]	2012	Arterioscler Thromb Vasc Biol. 32: 1104-1115. doi: 10.1161/ATVBAHA.111.237693. Epub 2012 Mar 1.	Atherosclerosis is a chronic inflammatory disorder that is the underlying cause of most cardiovascular disease. Both cells of the vessel wall and cells of the immune system participate in atherogenesis. This process is heavily influenced by plasma lipoproteins, genetics, and the hemodynamics of the blood flow in the artery. A variety of small and large animal models have been used to study the atherogenic process. No model is ideal as each has its own advantages and limitations with respect to manipulation of the atherogenic process and modeling human atherosclerosis or lipoprotein profile. Useful large animal models include pigs, rabbits, and nonhuman primates. Due in large part to the relative ease of genetic manipulation and the relatively short time frame for the development of atherosclerosis, murine models are currently the most extensively used. Although not all aspects of murine atherosclerosis are identical to humans, studies using murine models have suggested potential biological processes and interactions that underlie this process. As it becomes clear that different factors may influence different stages of lesion development, the use of mouse models with the ability to turn on or delete proteins or cells in tissue specific and temporal manner will be very valuable.	●	●								-		D	C
1466	実験動物（反復投与毒性）	Goldenthal, E. I.; Jessup, D. C.; Geil, R. B.; Mehring, J. S.	Ninety-Day Subacute Rhesus Monkey Toxicity Study(Study No. 137-087)	1979	US EPA Public Docket AR226-0447	No abstract available	●	●					●			企業データ		D	D

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①D	文献クラン②C
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1467	実験動物（心血管系）	Oppi, S.; Lüscher, T. F.; Stein, S.	Mouse models for atherosclerosis research-Which is my line? [Review]	2019	Front Cardiovasc Med. 2019 Apr 12;6:46. doi: 10.3389/fcvm.2019.00046. eCollection 2019.	Atherosclerosis is one of the primary causes of cardiovascular disease and mortality. This chronic immunometabolic disease evolves during decades in humans and encompasses different organs and immune cell types, as well as local and systemic processes that promote the progression of the disease. The most frequently used animal model to study these atherogenic processes and inter-organ crosstalk in a short time frame are genetically modified mouse models. Some models have been used throughout the last decades, and some others been developed recently. These models have important differences in cholesterol and lipoprotein metabolism, reverse cholesterol transport pathway, obesity and diabetes as well as inflammatory processes. Therefore, the disease develops and progresses differently in the various mouse models. Since atherosclerosis is a multifaceted disease and many processes contribute to its progression, the choice of the right mouse model is important to study specific aspects of the disease. We will describe the different mouse models and provide a roadmap to facilitate current and future atherosclerosis researchers to choose the right model depending on their scientific question.	●	●								-		D	C
1468	実験動物（免疫毒性）	Cook, T. M.; Protheroe, R. T.; Handel JM	Tetanus: a review of the literature	2001	Br J Anaesth. 87: 477-487. doi: 10.1093/bja/87.3.477	Tetanus is now a rare disease in the developed world. However, it remains an important cause of death worldwide and is associated with a high case mortality, particularly in the developing world. There are an estimated 800 000–1000 000 deaths from tetanus each year.28 Although the incidence in developed countries is low, the mortality in the group most at risk of contracting the illness, patients over 60 yr, remains above 50%.78 Modern intensive care management should prevent death from acute respiratory failure,109 but cardiovascular complications as a result of autonomic instability and other causes of death remain problematic. In this article, we review the epidemiology, pathophysiology, clinical features, and current management of tetanus.	●	●								-		C	C
1469	実験動物（免疫毒性）	Dewitt, J. C.; Copeland, C. B.; Luebke, R. W.	Suppression of humoral immunity by perfluorooctanoic acid is independent of elevated serum corticosterone concentration in mice	2009	Toxicol Sci. 109: 106-112. doi: 10.1093/toxsci/kfp040. Epub 2009 Feb 23.	The T-cell-dependent antibody response is suppressed in mice exposed to 3.75, 7.5, 15, and 30 mg PFOA (perfluorooctanoic acid)/kg body weight (bw). Reduced bw accompanied immunosuppression at 15 and 30 mg/kg. We investigated the hypothesis that the observed immunosuppression is secondary to elevated serum corticosterone levels by assessing immune function in adrenalectomized (adx) or sham-operated C57BL/6N female mice exposed to 0, 7.5, or 15 mg PFOA/kg bw in drinking water for 10 days. Bw, primary antibody responses to a T-dependent antigen, clinical serum chemistries related to liver health, and serum corticosterone levels were evaluated. Exposure to 15 mg/kg decreased bw by approximately 0.1 after 8 days of dosing and until 2 days postdosing in both adx and sham animals; bw of adx animals were still reduced 5 days postdosing. IgM antibody titers were statistically reduced by 0.15 in sham animals and 0.18 in adx animals exposed to 15 mg/kg and by 0.118 in adx animals exposed to 7.5 mg/kg. Corticosterone concentrations were elevated by 1.57 in dosed sham animals relative to control animals and were reduced by 0.27 in dosed adx animals relative to control animals (neither changes were statistically significant). Clinical serum chemistries related to liver health were not statistically altered by either dose or adrenalectomy. The failure of adrenalectomy to protect mice from the immunosuppressive effects of PFOA indicates that suppression of antibody synthesis is not the result of liver toxicity or stress-related corticosterone production.	●	●	●	●					●	-		B	B
1470	実験動物（免疫毒性）	Dewitt, J. C.; Copeland, C. B.; Strynar, M. J.; Luebke, R. W.	Perfluorooctanoic acid-induced immunomodulation in adult C57BL/6J or C57BL/6N female mice	2008	Environ Health Perspect. 2008 May;116(5):644-50. doi: 10.1289/ehp.10896.	BACKGROUND: Perfluorooctanoic acid (PFOA), an environmentally persistent compound of regulatory concern, has been reported to reduce antibody responses in mice at a single dose.OBJECTIVE: The aim of this study was to evaluate PFOA effects on humoral and cellular immunity using standard assays for assessing immune function, and to derive dose-response data.METHODS: C57BL/6J mice received 0 or 30 mg PFOA/kg/day for 10 days; half of the exposed groups were switched to vehicle and half continued on PFOA for five days. C57BL/6N mice received 0-30 mg/kg/day of PFOA in drinking water for 15 days. Mice were immunized with sheep red blood cells or sensitized to bovine serum albumin in Freund's complete adjuvant on day 10 of exposure; immune responses were determined 1 day post-exposure.RESULTS: We found that 30 mg PFOA/kg/day given for 10 or 15 days reduced IgM synthesis; serum collected 1 day postexposure contained 8.4 x 10(4) or 2.7 x 10(5) ng PFOA/mL, respectively. IgM synthesis was suppressed at exposures > or = 3.75 mg PFOA/kg/day in a dose-dependent manner, and IgG titers were elevated at 3.75 and 7.5 mg PFOA/kg/day. Serum PFOA at 3.75 mg/kg/day was 7.4 x 10(4) ng/mL 1 day postexposure, or 150-fold greater than the levels reported in individuals living near a PFOA production site. Using a second-degree polynomial model, we calculated a benchmark dose of 3 mg/kg/day, with a lower bound (95% confidence limit) of 1.75 mg/kg/day. Cell-mediated function was not affected.CONCLUSIONS: IgM antibodies were suppressed after PFOA exposure. The margin of exposure for reduced IgM antibody synthesis was approximately 150 for highly exposed human populations.	●	●	●	●		●	●		●	-	1	A	B
1471	実験動物（免疫毒性）	Dewitt, J. C.; Williams, W. C.; Creech, N. J.; Luebke, R. W.	Suppression of antigen-specific antibody responses in mice exposed to perfluorooctanoic acid: Role of PPARα and T- and B-cell targeting	2016	J Immunotoxicol. 13: 38-45. doi: 10.3109/1547691X.2014.996682. Epub 2015 Jan 16.	Abstract T-cell-dependent antibody responses (TDAR) are suppressed in female C57BL/6N mice exposed to ≥3.75 mg/kg of perfluorooctanoic acid (PFOA) for 15 days. To determine if suppression of humoral immunity by PFOA is peroxisome proliferator activated receptor alpha (PPARα)-dependent and if suppression is associated with specific targeting of T- or B-cells, three separate experiments were conducted: -1 female PPARα constitutive knockout (PPARα KO; B6.129S4-Ppar(tm1Gonz)N12) and wild-type controls (WT; C57BL/6-Tac) exposed to 0, 7.5, or 30 mg PFOA/kg for 15 days were immunized on Day 11 with a T-cell-dependent antigen and sera then collected for measures of antigen-specific IgM titers (TDAR) 5 days later; -2 female C57BL/6N WT mice exposed to 0, 0.94, 1.88, 3.75, or 7.5 mg PFOA/kg for 15 days were immunized with a T-cell-independent antigen on Day 11 and sera were then collected for analyses of antigen-specific IgM titers (TIAR) 7 days later; and -3 splenic lymphocyte phenotypes were assessed in unimmunized female C57BL/6N WT mice exposed to 0, 3.75, or 7.5 mg PFOA/kg for 10 days to investigate effects of PFOA in the absence of specific immunization. Separate groups of mice were immunized with a T-cell-dependent antigen after 11 days of exposure and splenic lymphocyte sub-populations were assessed after 13 or 15 days of exposure to assess numbers of stimulated cells. The results indicated that exposure to ≥1.88 mg PFOA/kg suppressed the TIAR; exposure to 30 mg PFOA/kg suppressed the TDAR in both PPARα KO and WT mice. The percentage of splenic B-cells was unchanged. Results obtained in the PPARα KO mice indicated that PPARα suppression of TDAR was independent of PPARα involvement. Suppression of the TIAR and the TDAR with minimal lymphocyte sub-population effects suggested that effects on humoral immunity are likely mediated by disruption of B-cell/plasma cell function.	●	●	●	●					●	-		B	B
1472	実験動物（免疫毒性）	Dong, G. H.; Zhang, Y. H.; Zheng, L.; Liu, W.; Jin, Y. H.; He, Q. C.	Chronic effects of perfluorooctanesulfonate exposure on immunotoxicity in adult male C57BL/6 mice	2009	Arch Toxicol. 2009 Sep;83(9):805-15. doi: 10.1007/s00204-009-0424-0. Epub 2009 Apr 3.	A paucity of data exists to corroborate the few studies that report immune suppression after exposure to perfluorooctanesulfonate (PFOS). In this study, adult male C57BL/6 mice were exposed to PFOS daily via gavage for 60 days [0, 0.5, 5, 25, 50, or 125 mg/kg total administered dose (TAD)]. The results showed that liver mass was significantly increased at > or 5 mg PFOS/kg TAD and in a dose-dependent manner. Lymphocyte proliferation and natural killer cell activity were altered in male mice. Plaque forming cell (PFC) response was suppressed beginning at 5 mg/kg TAD. Based on the liver mass and PFC response, the no observed adverse effect level and lowest observed adverse effect level for male mice exposed PFOS for 60 days was 0.5 and 5 mg/kg TAD, respectively. Measured PFOS serum concentrations at these dose levels were 0.674 +/- 0.166 and 7.132 +/- 1.039 mg/l, respectively. These results indicate that PFOS exposure can affect the immunity function in mice at levels approximately 50-fold for highly exposed human populations.	●	●	●	●	●		●		●	-	1	A	B
1473	実験動物（免疫毒性）	Lee, J.; Lee, S.; Choi, Y. A.,e; Jin, M.; Kim, Y. Y.; Kang, B. C.; Kim, M.; Dhakal, H.; Lee, S.; Kim, S.; Khang, D.; Kim, S. H.	Perfluorooctane sulfonate exacerbates mast cell-mediated allergic inflammation by the release of histamine	2018	Mol Cell Toxicol. 14, pages173–181 (2018), doi: 10.1007/s13273-018-0019-z	Backgrounds: Mast cells play a major role in allergic inflammation by the release of histamine, an important mediator of type I hypersensitivity. Concerns regarding potential harmful effects of perfluorooctane sulfonate (PFOS) have been raised. Previous studies reported that PFOS causes various adverse effects such as immunotoxicity and neurotoxicity. This report studied whether PFOS affects mast cells-mediated allergic inflammation. Methods: Ovalbumin-induced active systemic anaphylaxis model was used to assess for the type I hypersensitivity. After sensitization, mice were orally administered with PFOS and then allergic symptoms such as hypothermia and increase of serum allergic mediator were measured. In additional, this study investigated whether PFOS deteriorate allergic inflammation in immunoglobulin E-stimulated mast cells. Results: PFOS aggravated the allergic symptoms such as hypothermia, and increase of serum histamine, tumor necrosis factor-alpha and immunoglobulin (Ig) E/G(1). PFOS increased the release of histamine and beta-hexosaminidase through the up-regulation of intracellular calcium in IgE-stimulated mast cells. PFOS also enhanced the gene expression of pro-inflammatory cytokines by activating nuclear factor-kappa B. Conclusion: This study demonstrated that PFOS more intensifies the mast cell-mediated allergic inflammation.	●									-		B	B
1474	実験動物（免疫毒性）	Loveless, Scott E; Hoban, Denise; Sykes, Greg; Frame, Steven R; Everds, Nancy E	Evaluation of the immune system in rats and mice administered linear ammonium perfluorooctanoate	2008	Toxicol Sci. 2008 Sep;105(1):86-96. doi: 10.1093/toxsci/kfn113. Epub 2008 Jun 16.	Repeated high doses of ammonium perfluorooctanoate (APFO) have been reported to affect immune system function in mice. To examine dose-response characteristics in both rats and mice, male CD rats and CD-1 mice were dosed by oral gavage with 0.3-30 mg/kg/day of linear APFO for 29 days. Anti-sheep red blood cell (SRBC) IgM levels, clinical signs, body weights, selected hematology, and lipid parameters, liver weights, spleen, and thymus weights and cell number, selected histopathology, and serum corticosterone concentrations were evaluated. In rats, linear APFO had no effect on production of anti-SRBC antibodies. Ten and 30 mg/kg/day resulted in systemic toxicity as evidenced by decreases in body weight gain to 74 and 37%, and increases in serum corticosterone levels to 135 and 196% of control, respectively. In mice dosed with 10 and 30 mg/kg/day, marked systemic toxicity and stress were observed, as evidenced by a loss in body weight of 3.8 and 6.6 g, respectively (despite a tripling of liver weight), approximately 230% increase in serum corticosterone, and increases in absolute numbers of peripheral blood neutrophils and monocytes with an accompanying decrease in absolute lymphocyte numbers. Immune-related findings at 10 and 30 mg/kg/day that likely represent secondary responses to the systemic toxicity and stress observed at these doses include: decreased IgM antibody production at 10 (20% suppression) and 30 mg/kg/day (28% suppression); decreased spleen and thymus weights and cell numbers; microscopic depletion/atrophy of lymphoid tissue at 10 (thymus) and 30 mg/kg/day (spleen). In summary, no immune-related changes occurred in rats, even at doses causing systemic toxicity. In mice, immune-related changes occurred only at doses causing significant and profound systemic toxicity and stress.	●	●	●	●		●			●	-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献クラン①抽出	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1475	実験動物（免疫毒性）	Lv, Q. Y.; Wan, B.; Guo, L. H.; Yang, Y.; Ren, X. M.; Zhang, H.	In vivo immunotoxicity of perfluorooctane sulfonate in BALB/c mice: Identification of T-cell receptor and calcium-mediated signaling pathway disruption through gene expression profiling of the spleen	2015	Chem Biol Interact. 240: 84-93. doi: 10.1016/j.cbi.2015.07.015. Epub 2015 Aug 20.	Perfluorooctane sulfonate (PFOS) is a persistent organic pollutant that is used worldwide and is continuously being detected in biota and the environment, thus presenting potential threats to the ecosystem and human health. Although PFOS is highly immunotoxic, its underlying molecular mechanisms remain largely unknown. The present study examined PFOS-induced immunotoxicity in the mouse spleen and explored its underlying mechanisms by gene expression profiling. Oral exposure of male BALB/c mice for three weeks followed by one-week recovery showed that a 10 mg/kg/day PFOS exposure damaged the splenic architecture, inhibited T-cell proliferation in response to mitogen, and increased the percentages of T helper (CD3(+)CD4(+)) and cytotoxic T (CD3(+)CD8(+)) cells, despite the decrease in the absolute number of these cells. A delayed type of PFOS immunotoxicity was observed, which mainly occurred during the recovery period. Global gene expression profiling of mouse spleens and QRT-PCR analyses suggest that PFOS inhibited the expression of genes involved in cell cycle regulation and NRF2-mediated oxidative stress response, and upregulated those in TCR signaling, calcium signaling, and p38/MAPK signaling pathways. Western blot analysis confirmed that the expressions of CAMK4, THEMIS, and CD3G, which were involved in the upregulated pathways, were induced upon PFOS exposure. Acute PFOS exposure modulated calcium by PFOS treatment as revealed in the present study might facilitate in better understanding PFOS immunotoxicity and explain the association between immune disease and PFOS exposure.	●	●		●						-		B	B
1476	実験動物（免疫毒性）	Peden-Adams, M. M.; Keller, J. M.; Eudaly, J. G.; Berger, J.; Gilkeson, G. S.; Keil, D. E.	Suppression of humoral immunity in mice following exposure to perfluorooctane sulfonate	2008	Toxicol Sci. 2008 Jul;104(1):144-54. doi: 10.1093/toxsci/kfn059. Epub 2008 Mar 20.	Adult male and female B6C3F1 mice were exposed to perfluorooctane sulfonate (PFOS) daily via gavage for 28 days (0, 0.005, 0.05, 0.1, 0.5, 1, or 5 mg/kg total administered dose [TAD]). Following exposure, various immune parameters were assessed and serum PFOS concentrations were determined. Lymphocyte proliferation was not altered in either gender. Natural killer cell activity was increased compared with control at 0.5, 1, and 5 mg/kg TAD in male mice but was not altered in female mice. At these treatment levels, splenic T-cell immunophenotypes were minimally altered in females, but all T-cell subpopulations were significantly modulated in males beginning at 0.1 mg/kg TAD. The sheep red blood cell (SRBC) plaque-forming cell (PFC) response was suppressed in male mice beginning at 0.05 mg/kg TAD and in females at 0.5 mg/kg TAD. Serum trinitrophenyl (TNP)-specific IgM titers were also decreased by PFOS after TNP-LPS (TNP conjugated to lipopolysacharide) challenge suggesting that the humoral immune effects may be attributed to the B-cell rather than T-cell because both T-dependent (SRBC) and T-independent (TI) (TNP-LPS) antigens result in suppressed IgM production. Based on the PFC response, the low observed effect level (LOEL) for males was 0.05 mg/kg TAD (ED(50) = 0.021 mg/kg TAD) and for females was 0.5 mg/kg TAD (ED(50) = 0.59 mg/kg TAD). Measured PFOS serum concentrations at these dose levels were 91.5 +/- 22.2 ng/g and 666 +/- 108 ng/g (mean +/- SD), respectively. The male LOEL serum level was approximately 14-fold lower than reported mean blood levels from occupationally exposed humans and fell in the upper range of concentrations reported for the general population. Overall, this study provides a profile of PFOS immunotoxicity showing effects at levels reported in humans and identifies the B-cells as a potential target.	●	●	●	●			●		●	-	1	A	B
1477	実験動物（免疫毒性）	Qazi, M. R.; Bogdanska, J.; Butenhoff, J. L.; Nelson, B. D.; Depierre, J. W.; Abedi-Valugerdi, M.	High-dose, short-term exposure of mice to perfluorooctanesulfonate (PFOS) or perfluorooctanoate (PFOA) affects the number of circulating neutrophils differently, but enhances the inflammatory responses of macrophages to lipopolysaccharide (LPS) in a similar fashion	2009	Toxicology. 2009 Aug 21;262(3):207-14. doi: 10.1016/j.tox.2009.06.010. Epub 2009 Jun 21.	Having found previously that high-dose, short-term dietary exposure of mice to perfluorooctanesulfonate (PFOS) or perfluorooctanoate (PFOA) suppresses adaptive immunity, in the present study we characterize the effects of these fluorochemicals on the innate immune system. Male C57BL/6 mice receiving 0.0002 (w/w) PFOS or PFOA in their diet for 10 days exhibited a significant reduction in the numbers of total white blood cells (WBC), involving lymphopenia in both cases, but neutropenia only in response to treatment with PFOA. Moreover, both compounds also markedly reduced the number of macrophages (CD11b(+) cells) in the bone marrow, but not in the spleen or peritoneal cavity. The ex vivo production of tumor necrosis factor-alpha (TNF-alpha) and interleukin 6 (IL-6) by peritoneal macrophages isolated from animals treated with PFOA or PFOS was increased modestly. Moreover, both fluorochemicals markedly enhanced the ex vivo production of these same cytokines by peritoneal and bone marrow macrophages stimulated either in vitro or in vivo with lipopolysaccharide (LPS); whereas there was no such effect on splenic macrophages. The serum levels of these inflammatory cytokines observed in response to in vivo stimulation with LPS were elevated substantially by prior exposure to PFOA, but not by PFOS. None of these parameters of innate immunity were altered in animals receiving a dietary dose of these compounds that was 20-fold lower (0.001%, w/w). These findings reveal that in addition to suppressing adaptive immunity, high-dose, short-term exposure of mice to either PFOS or PFOA augments inflammatory responses to LPS, a potent activator of innate immunity.	●	●	●	●	●	●			●	-		B	B
1478	実験動物（免疫毒性）	Qazi, M. R.; Xia, Z.; Bogdanska, J.; Chang, S. C.; Ehresman, D. J.; Butenhoff, J. L.; Nelson, B. D.; Depierre, J. W.; Abedi-Valugerdi, M.	The atrophy and changes in the cellular compositions of the thymus and spleen observed in mice subjected to short-term exposure to perfluorooctanesulfonate are high-dose phenomena mediated in part by peroxisome proliferator-activated receptor-alpha (PPARalpha)	2009	Toxicology. 260: 68-76. doi: 10.1016/j.tox.2009.03.009. Epub 2009 Mar 24.	We have previously shown that short-term, high-dose exposure of mice to the environmentally persistent perfluorooctanoate (PFOA) results in thymic and splenic atrophy and the attenuation of specific humoral immune responses. Here we characterize the effects of a 10-day treatment with different dietary doses (1-0.001%, w/w) of perfluorooctanesulfonate (PFOS), a similar fluorochemical, on the immune system of male C57BL/6 mice. At doses greater than 0.02%, PFOS induced clinical signs of toxicity in the animals, whereas at the concentration of 0.02%, this compound caused weight loss, hepatomegaly and atrophy of the thymus, spleen and adipose tissue without toxicity. With this latter dose, histopathological and flow-cytometric analysis revealed that (i) the thymic cortex was virtually depleted of cells; (ii) the total numbers of thymocytes and splenocytes were reduced by 84 and 43%, respectively; (iii) although all populations of thymocytes and splenocytes were smaller, the thymic CD4(+)CD8(+) cells and the splenic B-lymphocytes were most decreased. These alterations resembled those evoked by analogous exposure to PFOA, but were less pronounced. At lower doses (less than 0.02%), PFOS induced hepatomegaly without affecting the thymus or spleen. Finally, comparison of male wild-type 129/Sv mice and the corresponding knock-outs lacking peroxisome proliferator-activated receptor-alpha (PPARalpha) indicated that these effects of PFOS are not strain-dependent. More importantly, hepatomegaly is independent of PPARalpha, the thymic changes are partially dependent on this receptor, and splenic responses are largely eliminated in its absence. Thus, immunomodulation caused by PFOS is a high-dose phenomenon partially dependent on PPARalpha, of PFOS are not strain-dependent. More importantly, hepatomegaly is independent of PPARalpha, the thymic changes are partially dependent on this receptor, and splenic responses are largely eliminated in its absence. Thus, immunomodulation caused by PFOS is a high-dose phenomenon partially dependent on PPARalpha.	●	●	●	●	●				●	-		B	B
1479	実験動物（免疫毒性）	Son, H. Y.; Lee, S.; Tak, E. N.; Cho, H. S.; Shin, H. I.; Kim, S. H.; Yang, J. H.	Perfluorooctanoic acid alters T lymphocyte phenotypes and cytokine expression in mice	2009	Environ Toxicol. 2009 Dec;24(6):580-8. doi: 10.1002/tox.20459.	Perfluorooctanoic acid (PFOA) has been used in commercial applications and detected in environmental matrices. This study focuses on whether PFOA affects the function of immune organs (spleen and thymus). Male ICR mice were exposed to 0, 2, 10, 50, and 250 ppm of PFOA in drinking water for 21 days. PFOA differently altered T lymphocyte populations. In the spleen, all doses of PFOA decreased CD8(+) lymphocytes; CD4(+) lymphocytes were increased by 50 and 250 ppm of PFOA. Exposure to 250 ppm of PFOA increased CD8(+) lymphocytes in the thymus. In the histopathological evaluation, the spleen of 250 ppm PFOA-treated groups revealed the increase of lymphoid hyperplasia of white pulp without significant alteration of red pulp. The thymus of 250 ppm PFOA-treated group showed decreased thickness of the cortex and medulla, but lymphoid cells were more densely arranged. PFOA elevated the expression of proinflammatory cytokines (tumor necrosis factor alpha, interleukin-1beta, and interleukin-6) in the spleen, and proto-oncogene, c-myc, in the spleen and thymus. In conclusion, our data demonstrated that PFOA has an immunomodulatory effect by altering T lymphocyte phenotypes and gene expression of proinflammatory cytokines.	●	●	●	●		●			●	-	1	A	B
1480	実験動物（免疫毒性）	Yang, Q.; Xie, Y.; Alexson, S. E.; Nelson, B. D.; Depierre, J. W.	Involvement of the peroxisome proliferator-activated receptor alpha in the immunomodulation caused by peroxisome proliferators in mice	2002	Biochem Pharmacol. 63: 1893-1900. doi: 10.1016/s0006-2952(02)00923-1.	Peroxisome proliferators (PPs) are a large class of structurally diverse chemicals, which includes drugs designed to improve the metabolic abnormalities linking hypertriglyceridemia to diabetes, hyperglycemia, insulin-resistance and atherosclerosis. We have recently demonstrated that exposure of rodents to potent PPs indirectly causes a number of immunomodulating effects, resulting in severe adaptive immunosuppression. Since the peroxisome proliferator-activated receptor alpha (PPARalpha) plays a central role in mediating the pleiotropic responses exerted by PPs, we have compared here the immunomodulating effects of the PPs perfluorooctanoic acid (PFOA) and Wy-14,643 in wild-type and PPARalpha-null mice. The reductions in spleen weight and in the number of splenocytes caused by PP treatment in wild-type mice was not observed in PPARalpha-null mice. Furthermore, the reductions in thymus weight and in the number of thymocytes were potently attenuated in the latter animals. Similarly, the dramatic decreases in the size of the CD4(+)CD8(+) population of cells in the thymus and in the number of thymocytes in the S and G2/M phases of the cell cycle observed in wild-type mice administered PPs were much less extensive in PPARalpha-null mice. Finally, in contrast to the case of wild-type animals, the response of splenocytes isolated from the spleen of PP-treated PPARalpha-null mice to appropriate T- or B-cell activators in vitro was not reduced. Altogether, these data indicate that PPARalpha plays a major role in the immunomodulation caused by PPs. The possible relevance of these changes to the alterations in plasma lipids also caused by PPs is discussed.	●	●		●		●				-		B	B
1481	実験動物（免疫毒性）	Yang, Q; Xie, Y; Depierre, J W	Effects of peroxisome proliferators on the thymus and spleen of mice	2000	Clin Exp Immunol. 2000 Nov;122(2):219-26. doi: 10.1046/j.1365-2249.2000.01367.x.	The effects of peroxisome proliferators on the immune system of male C57B1/6 mice have been investigated. Significant atrophy of the thymus and spleen was observed in animals treated with potent peroxisome proliferators (e.g. perfluorooctanoic acid (PFOA), di(2-ethylhexyl)phthalate (DEHP), Wy-14643 and nafenopin), whereas the effects of a moderate peroxisome proliferator (i.e. acetylsalicylic acid (ASA)) were relatively weak. The time course of thymic and splenic atrophy caused by PFOA was found to resemble the time course of the increase in liver weight and of peroxisome proliferation. Analysis of the numbers and phenotypes of thymocytes and splenocytes from PFOA-treated mice revealed the following: (i) the numbers of thymocytes and splenocytes were decreased > 90% and about 50%, respectively, by PFOA treatment; (ii) although all populations of thymocytes were decreased, the immature CD4+CD8+ population was decreased most dramatically; (iii) the numbers of both T and B cells in the spleen were decreased by PFOA treatment. Analysis of the cell cycle of thymocytes indicated that the thymic atrophy caused by PFOA in mice results, at least in part, from inhibition of thymocyte proliferation. Interestingly, in vitro exposure to PFOA for up to 24 h did not produce analogous effects in either thymocytes or splenocytes. Thus, the thymic and splenic atrophy caused by PFOA appears to involve an indirect pathway.	●	●		●						-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報抽出対象	文献ランク①	文献ランク②
1482	実験動物（免疫毒性）	Yang, Q.; Xie, Y.; Eriksson, A. M.; Nelson, B. D.; Depierre, J. W.	Further evidence for the involvement of inhibition of cell proliferation and development in thymic and splenic atrophy induced by the peroxisome proliferator perfluorooctanoic acid in mice	2001	Biochem Pharmacol. 2001 Oct 15;62(8):1133-40. doi: 10.1016/s0006-2952(01)00752-3.	We recently demonstrated that severe thymic and splenic atrophy occur upon dietary treatment of mice with potent peroxisome proliferators (PPs), e.g. perfluorooctanoic acid (PFOA), WY-14,643, nafenopin, and di(2-ethylhexyl)phthalate (DEHP). In the present study, we investigated this phenomenon further employing a relative inert PP, PFOA. Comparison of the dose-dependencies and time-courses indicated that the peroxisome proliferative effect occurred prior to atrophy of both the thymus and spleen. However, following withdrawal of PFOA from the diet, the weight of the thymus and spleen rapidly returned to normal within 10 and 5 days, respectively, in contrast to the more persistent peroxisome proliferation. Furthermore, the changes in thymus and spleen weight upon PFOA treatment and the following withdrawal from diet paralleled the changes in total thymocyte and splenocyte counts, respectively. It was found previously that the decreases in the thymocyte populations present in the S and G2/M phases, as well as in the number of CD4+CD8+ cells upon PFOA treatment, were the most dramatic, perhaps reflecting inhibition of thymocyte proliferation in connection with thymocyte development. Here, the recovery of thymocytes began with increases in the populations in these same phases of the cell cycle, with CD4+CD8+ cells recovering most rapidly, lending further support to our previous hypothesis. The possible relationship of these immunotoxic effects of PPs to the changes they cause in fatty acid metabolism is discussed.	●	●		●		●				-		B	B
1483	実験動物（免疫毒性）	Zheng, L.; Dong, G. H.; Jin, Y. H.; He, Q. C.	Immunotoxic changes associated with a 7-day oral exposure to perfluorooctanesulfonate (PFOS) in adult male C57BL/6 mice	2009	Arch Toxicol. 2009 Jul;83(7):679-89. doi: 10.1007/s00204-008-0361-3. Epub 2008 Oct 21.	Perfluorooctanesulfonate (PFOS) is a widespread contaminant in the environment, as well as in wildlife and in humans. Toxicity tests in rodents have raised concerns about potential developmental, reproductive, and systemic effects of PFOS. However, there is little information about the effect of PFOS on immune system. In this study, adult male C57BL/6 mice were given by gavage 0, 5, 20 or 40 mg PFOS/kg day(-1) for 7 days. The results showed that PFOS exposure decreased food intake and body weight and increased liver mass and serum corticosterone levels in a dose-dependent manner. Flow cytometry analysis showed that the number of lymphocytic subpopulation cells decreased significantly in 20 or 40 mg PFOS/kg day(-1) group in comparison with normal C57BL/6 mice. Treatment with PFOS also markedly depressed the natural killer (NK) cell activity, lymphocyte proliferation and the plaque-forming cell (PFC) response. These results indicate that PFOS exposure can affect the immunity function in mice.	●	●	●	●					●	-	1	A	B
1484	MOA（免疫毒性）	Brieger, Anne; Bienefeld, Nicole; Hasan, Rafah; Goerlich, Roland; Haase, Hajo	Impact of perfluorooctane sulfonate and perfluorooctanoic acid on human peripheral leukocytes	2011	Toxicol In Vitro. 2011 Jun;25(4):960-8. doi: 10.1016/j.tiv.2011.03.005. Epub 2011 Mar 21.	Perfluorinated compounds (PFCs), such as perfluorooctanesulfonate (PFOS) and perfluorooctanoic acid (PFOA), are xenobiotics that can be detected worldwide in the environment, wildlife, and humans. So far, the immunotoxicity of PFCs has only been investigated in rodents, but not in humans. In this study, we explore the impact of PFOS and PFOA on selected functions of human leukocytes in vitro. PFOS induced a significant decrease of natural killer-cell activity and reduced the release of the pro-inflammatory cytokine TNF-α following lipopolysaccharide (LPS)-stimulation. Furthermore, the plasma PFOS concentrations (2.09-8.98 ng/ml) found in our study subjects correlated positively with the LPS-stimulated IL-6 release. PFOA augmented significantly calcitriol-induced monocytic differentiation of the HL-60 cell line. Additionally, there was a significant linear relationship between LPS-stimulated TNF-α and IL-6 release, and the plasma PFOA (1.20-6.92ng/ml) concentrations of the study subjects. In conclusion, the investigated PFCs affect human immune cells mainly with regard to natural killer-cell cytotoxicity and the pro-inflammatory cytokine release by stimulated macrophages.			●							-		B	B
1485	MOA（免疫毒性）	Corsini, Emanuela; Avogadro, Anna; Galbiati, Valentina; dell'Agli, Mario; Marinovich, Marina; Galli, Corrado L; Germolec, Dori R	In vitro evaluation of the immunotoxic potential of perfluorinated compounds (PFCs)	2011	Toxicol Appl Pharmacol. 2011 Jan 15;250(2):108-16. doi: 10.1016/j.taap.2010.11.004. Epub 2010 Nov 12.	There is evidence from both epidemiology and laboratory studies that perfluorinated compounds may be immunotoxic, affecting both cell-mediated and humoral immunity. The overall goal of this study was to investigate the mechanisms underlying the immunotoxic effects of perfluorooctane sulfonate (PFOS) and perfluorooctane acid (PFOA), using in vitro assays. The release of the pro-inflammatory cytokines IL-6, IL-8, and TNF-α was evaluated in lipopolysaccharide (LPS)-stimulated human peripheral blood leukocytes and in the human promyelocytic cell line THP-1, while the release of IL-4, IL-10 and IFN-γ was evaluated in phytohaemagglutinin (PHA)-stimulated peripheral blood leukocytes. PFOA and PFOS suppressed LPS-induced TNF-α production in primary human cultures and THP-1 cells, while IL-8 was suppressed only in THP-1 cells. IL-6 release was decreased only by PFOS. Both PFOA and PFOS decreased T-cell derived, PHA-induced IL-4 and IL-10 release, while IFN-γ release was affected only by PFOS. In all instances, PFOS was more potent than PFOA. Mechanistic investigations carried out in THP-1 cells demonstrated that the effect on cytokine release was pre-transcriptional, as assessed by a reduction in LPS-induced TNF-α mRNA expression. Using siRNA, a role for PPAR-α could be demonstrated for PFOA-induced immunotoxicity, while an inhibitory effect on LPS-induced I-κB degradation could explain the immunomodulatory effect of PFOS. The dissimilar role of PPAR-α in PFOA and PFOS-induced immunotoxicity was consistent with the differing effects observed on LPS-induced MMP-9 release: PFOA, as the PPAR-α agonist fenofibrate, modulated the release, while PFOS had no effect. Overall, these studies suggest that PFCs directly suppress cytokine secretion by immune cells, and that PFOA and PFOS have different mechanisms of action.			●							-		B	B
1486	実験動物（免疫毒性）	Dong, Guang-Hui; Liu, Miao-Miao; Wang, Da; Zheng, Li; Liang, Zai-Fu; Jin, Yi-He	Sub-chronic effect of perfluorooctanesulfonate (PFOS) on the balance of type 1 and type 2 cytokine in adult C57BL6 mice	2011	Arch Toxicol. 2011 Oct;85(10):1235-44. doi: 10.1007/s00204-011-0661-x. Epub 2011 Feb 16.	As a ubiquitous and highly persistent environmental contaminant, the clear mechanisms to explain any perfluorooctanesulfonate (PFOS)-induced immunotoxicity are still unknown. This study here sought to examine the ability of PFOS to potentially perturb T-helper (T(H))-1 and T(H)-2 cell cytokine secreting activities, as well as to cause shifts in antibody isotype levels, and possible mechanisms involved in PFOS-induced immunotoxicity. Adult male C57BL/6 mice were exposed to PFOS daily via gavage for 60 days [0, 0.5, 1, 5, 25, or 50 mg/kg total administered dose (TAD)]. One day after the final exposure, the ex vivo production of the T(H)1-type cytokines (IL-2 and IFN-γ), T(H)2-type (IL-4), and IL-10 cytokines by isolated splenocytes, serum levels of immunoglobulin (Ig) were assessed via ELISA or ELISPOT. The results showed that IL-4 secretion was increased at exposure ≥5 mg PFOS/kg TAD in a dose-dependent manner. PFOS exposure increased IL-10 but decreased IL-2 and IFN-γ formation markedly at 50 mg PFOS/kg TAD. Serum levels of sheep red blood cells (SRBC)-specific IgM synthesis decreased significantly with PFOS exposure in a dose-related manner; serum SRBC-specific IgG, IgG1, and IgE levels increased with 50 mg PFOS/kg TAD regimens. These results indicated that, after a long-term exposure to PFOS, a host's immune state is likely to be characterized by a shift toward a more T(H)2-like state that, in turn, may lead to enhancement of their humoral response and suppression of their cellular response at levels of upper range for occupationally exposed workers or approximately 150-fold for general human population.			●	●	●				●	-		B	B
1487	実験動物（免疫毒性）	Dong, Guang-Hui; Wang, Jing; Zhang, Ying-Hua; Liu, Miao-Miao; Wang, Da; Zheng, Li; Jin, Yi-He	Induction of p53-mediated apoptosis in splenocytes and thymocytes of C57BL/6 mice exposed to perfluorooctane sulfonate (PFOS)	2012	Toxicol Appl Pharmacol. 2012 Oct 15;264(2):292-9. doi: 10.1016/j.taap.2012.08.010. Epub 2012 Aug 19.	Perfluorooctane sulfonate (PFOS) is a persistent environmental contaminant found in human and wildlife tissues. It has been reported that PFOS can cause atrophy of the immune organs and apoptosis of immunocytes in rodents. However, the mechanism behind such cause is still unclear. To understand the model of cell death and its mechanism on lymphoid cells in vivo, we conducted a dose/response experiment in which 4 groups of male adult C57BL/6 mice (12 mice per group) were dosed daily by oral gavage with PFOS at 0, 0.0167, 0.0833, or 0.8333mg/kg/day, yielding targeted Total Administered Dose (TAD) of 0, 1, 5, or 50mg PFOS/kg, respectively, over 60days. The results showed that spleen and thymus weight were significantly reduced in the highest PFOS-dose-group (TAD 50mg PFOS/kg) compared to the control group, whereas liver weight was significantly increased. We analyzed the cell death via apoptosis with an annexin-V/propidium iodide assay by flow cytometry, and observed that both the percentage of apoptosis and the expression of the pro-apoptotic proteins p53 in splenocytes and thymocytes increased in a dose-related manner after PFOS treatment. We also observed that PFOS induced p53-dependent apoptosis through the cooperation between the Bcl-xl down regulation without changing the Bcl-2 and Bax expression. The down regulation of Bcl-xl was strongly indicating mitochondrial involvement in apoptosis. It is confirmed by the release of cytochrome c and activation of caspase-3. All of these findings establish an important role of p53 and mitochondrial function in PFOS induced toxic environment in the host.			●		●				●	-		B	B
1488	実験動物（免疫毒性）	Fair, Patricia A; Driscoll, Erin; Mollenhauer, Meagan A M; Bradshaw, Sarah G; Yun, Se Hun; Kannan, Kurunthachalam; Bossart, Gregory D; Keil, Deborah E; Peden-Adams, Margie M	Effects of environmentally-relevant levels of perfluorooctane sulfonate on clinical parameters and immunological functions in B 6C 3F 1 mice	2011	J Immunotoxicol. 2011 Jan-Mar;8(1):17-29. doi: 10.3109/1547691X.2010.527868. Epub 2011 Jan 24.	In the first part of a series of studies to account for perfluorooctane sulfonate (PFOS)-induced sheep red blood cell (SRBC)-specific immunoglobulin M (IgM) antibody suppression in mice, a survey of clinical and immunotoxicological endpoints was examined. Adult female $B_6C_3F_1$ mice were exposed orally for 28 days to a total administered dose (TAD) of 0, 0.1, 0.5, 1, or 5 mg PFOS/kg. Uterus wet weight was significantly decreased compared with control at the 5 mg/kg dose. No indications of wasting syndrome, malnutrition, alteration of thyroid homeostasis, or signs of overt toxicity were observed. Numbers of splenic CD19+/CD21$^-$, CD19+/CD21+, B220+/CD40+, CD4+/CD154$^-$, CD4+/CD154+, and MHC-II+ cells were not altered. Additionally, ex vivo interleukin-4 (IL-4), IL-5, and IL-6 production by in vitro anti-CD3- or phorbol myristate acetate-stimulated CD4+ T-cells was not affected. Ex vivo IL-6 production by B-cells was significantly increased by in vitro stimulation with either anti-CD40 or lipopolysaccharide. Increased IL-6 production by B-cells was the most sensitive endpoint assessed resulting in alterations at the lowest dose tested (0.1 mg/kg TAD) following anti-CD40 stimulation. Further studies are required to characterize effects on inflammatory markers such as IL-6 at environmentally relevant concentrations of PFOS and to determine the key events associated with PFOS-induced IgM suppression to address potential human health risks.			●		●					-	1	A	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報抽出対象	文献ランク①	文献ランク②
1489	MOA（免疫毒性）	Fang, Xuemei; Zhang, Lianjun; Feng, Yixing; Zhao, Yong; Dai, Jiayin	Immunotoxic effects of perfluorononanoic acid on BALB/c mice	2008	Toxicol Sci. 2008 Oct;105(2):312-21. doi: 10.1093/toxsci/kfn127. Epub 2008 Jun 26.	The effects of perfluorononanoic acid (PFNA) on the immune system and its mechanism of action in mice have not been elucidated. Thus, BALB/c mice were exposed to the PFNA (0, 1, 3, or 5 mg/kg/day) for fourteen days. Exposure to PFNA led to a decrease in body weight and in the weight of the lymphoid organs. Cell cycle arrest and apoptosis were observed in the spleen and thymus following PFNA exposure. In the thymus, PFNA mostly modulated CD4+CD8+ thymocytes, whereas the F4/80+, CD11c+, and CD49b+ cells were major targets in the spleen. Although concanavalin A-induced T lymphocyte blastogenesis was not altered by PFNA, production of interleukin (IL)-4 and interferon-gamma by splenic lymphocytes was remarkably impaired. The levels of cortisol and adrenocorticotrophic hormone in sera were increased; however, the expression of glucocorticoid receptor in the thymus was unchanged. In addition, expression of the peroxisome proliferator-activated receptors (PPAR-alpha and PPAR-gamma) and IL-1beta were upregulated significantly in the thymus at a dose of 1 mg PFNA/kg/day. No significant changes in expression of the inhibitory protein IkappaBalpha and IkappaBalpha kinase were observed. Together, these results suggest that PFNA exerts toxic effects on lymphoid organs and T cell and innate immune cell homeostasis in mice and that these effects may result from the activation of PPAR-alpha, PPAR-gamma, and the hypothalamic-pituitary-adrenal axis. Interestingly, at the transcriptional level, the nuclear factor-kappa B signaling pathway appears to be uninvolved in the immunotoxic potential of PFNA.			●	●						-		C	B
1490	MOA（免疫毒性）	Fang, Xuemei; Feng, Yixing; Shi, Zhimin; Dai, Jiayin	Alterations of cytokines and MAPK signaling pathways are related to the immunotoxic effect of perfluorononanoic acid	2009	Toxicol Sci. 2009 Apr;108(2):367-76. doi: 10.1093/toxsci/kfp019. Epub 2009 Feb 5.	Perfluorononanoate (PFNA), a perfluorinated alkyl acid containing nine carbon chains, has been detected in abiotic and biotic matrices worldwide. Although a few studies have reported toxic effects of PFNA, little information of the mechanism has been offered. In this study, the effects of PFNA exposure on thymus and the related mechanisms were investigated. Male rats were orally dosed with 0, 1, 3, or 5 mg PFNA/kg/day for 14 days. A significant decrease of body weight and thymus weight were observed in the rats receiving 3 or 5 mg PFNA/kg/day. Histopathological examination revealed dose-dependent increases in thymocyte apoptosis. Rats receiving 3 or 5 mg PFNA/kg/day exhibited increased interleukin (IL)-1 and decreased IL-2 concentrations in sera, whereas elevated IL-4 and cortisol levels only occurred in the highest dose group. Quantitative real-time PCR indicated that expression of peroxisome proliferator-activated receptor alpha (PPAR-alpha) was increased in the thymi of all dosed rats, and a similar trend occurred for PPAR-gamma in the two highest dose groups. The mRNA levels of c-Jun NH(2)-terminal kinase (JNK), nuclear factor-kappa B, p65 subunit, and inhibitory protein IkappaBalpha were unchanged; however, increased and decreased mRNA levels of p38 kinase were found in rats exposed to 3 or 5 mg PFNA/kg/day, respectively. Decreased Bcl-2 mRNA levels were observed in rats receiving 5 mg PFNA/kg/day. A significant increase in protein levels of phospho-JNK was found in all PFNA-treated rats. Phospho-p38 was significantly enhanced in 1 and 3 mg PFNA/kg/day groups, whereas phospho-IkappaBalpha remained consistent in all rats studied. Together, these data suggested that apart from the activation of PPARs, PFNA exposure in rats lead to the alteration of serum cytokines, which subsequently activated mitogen-activated protein kinase signaling pathways and potentially modulated the immune system. Additionally, increased serum cortisol and decreased expression of Bcl-2 in thymus likely contributed to the PFNA-induced thymocyte apoptosis.			●	●						-		C	B
1491	実験動物（免疫毒性）	Guruge, Keerthi S; Hikono, Hirokazu; Shimada, Nobuaki; Murakami, Kenji; Hasegawa, Jun; Yeung, Leo W Y; Yamanaka, Noriko; Yamashita, Nobuyoshi	Effect of perfluorooctane sulfonate (PFOS) on influenza A virus-induced mortality in female B6C3F1 mice	2009	J Toxicol Sci. 2009 Dec;34(6):687-91. doi: 10.2131/jts.34.687.	Recent studies showed that perfluorooctane sulfonate (PFOS) affects the mammalian immune system at levels reportedly found in the general human population. It has been demonstrated that exposure to immunotoxic chemicals may diminish the host resistance of animals to various pathogenic challenges and enhance mortality. Therefore, the current study was carried out to characterize the effect of a 21 day pre-administration of zero, 5, or 25 microg PFOS/kg bw/day in female B6C3F1 mice on host resistance to influenza A virus infection. At the end of PFOS exposure, body/organ weights did not significantly change whereas PFOS distribution in blood plasma, spleen, thymus and lung was dose-dependently increased. PFOS exposure in mice resulted a significant increase in emaciation and mortality in response to influenza A virus. The effective plasma concentrations in female mice were at least several fold lower than reported mean blood PFOS levels from occupationally exposed humans, and fell in the upper range of blood concentrations of PFOS in the normal human population and in a wide range of wild animals. Hence, it should be important to clarify the precise mechanism(s) for excess mortality observed in the high dose group.			●	●	●				●	-	1	B	A
1492	実験動物（免疫毒性）	Lee, Jun-Kyoung; Kim, Sang-Hyun	Correlation between mast cell-mediated allergic inflammation and length of perfluorinated compounds	2018	J Toxicol Environ Health A. 2018;81(9):302-313. doi: 10.1080/15287394.2018.1440188. Epub 2018 Feb 26.	Perfluorinated compounds (PFC) have widely been used in numerous applications including clothing, food packaging, and nonstick coating. With the widespread use of PFC, concerns regarding potential adverse health effects in humans and wildlife have increased. In spite of the known PFC-mediated immunotoxiciy, correlation with PFC and allergic inflammation still requires elucidation. The aim of this study was to examine the effect of four types of PFC (perfluoroheptanoic acid [PFHpA], perfluorononanoic acid [PFNA], perfluorodecanoic acid [PFDA], and perfluoroundecanoic acid [PFUnA]) on mast cell-mediated allergic inflammation in the presence of high-affinity immunoglobulin (Ig) E receptor (FcεRI) cross-linking. Among PFC family, long-chain PFDA and PFUnA increased release of histamine and β-hexosaminidase by up-regulation of intracellular calcium levels in IgE-stimulated mast cells. In addition, PFDA and PFUnA enhanced gene expression of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and IL-8 by activation of nuclear factor-κB in IgE-stimulated mast cells. In ovalbumin (OVA)-induced model of systemic anaphylaxis in the presence of hypothermia, PFNA, PFDA, and PFUnA exacerbated allergic symptoms accompanied by elevation in serum histamine, TNF-α, IgE, and IgG(1). Our data indicate that some PFC aggravated high-affinity IgE receptor (FcεRI)-mediated mast cell degranulation and allergic symptoms. Consequently, the results demonstrated that carbon-chain length of PFC may serve as a factor in allergic inflammation.			●							-		B	B
1493	実験動物（免疫毒性）	Lefebvre, David E; Curran, Ivan; Armstrong, Cheryl; Coady, Laurie; Parenteau, Monique; Liston, Virginia; Barker, Michael; Aziz, Syed; Rutherford, Kathryn; Bellon-Gagnon, Pascale; Shenton, Jacintha; Mehta, Rekha; Bondy, Genevieve	Immunomodulatory effects of dietary potassium perfluorooctane sulfonate (PFOS) exposure in adult sprague-dawley rats	2008	J Toxicol Environ Health A. 2008;71(23):1516-25. doi: 10.1080/15287390802391943.	Perfluorooctanesulfonate (PFOS) is a stable and environmentally persistent metabolic or degradation product of perfluorooctanyl compounds that were manufactured for a variety of industrial and consumer applications. PFOS itself was sold for use as a surfactant. The structurally related contaminants perfluorooctanoic acid (PFOA), perfluorodecanoic acid (PFDA), and N-ethyl perfluorooctane sulfonamide (N-EtPFOSA) were shown to suppress immune responses in laboratory rodents. Relatively low doses of PFOS were found to be immunosuppressive in mice. To assess effects of PFOS on the rat immune system at doses known to alter hepatic function, changes in the morphology and function of immune tissues and cells were measured in adult rats exposed to PFOS in their diet for 28 d at levels ranging from 2 to 100 mg PFOS/kg diet (corresponding to approximately 0.14 to 7.58 mg/kg body weight [bw]/d) and compared to those receiving control diet. Body weight reductions were significant in male and female rats exposed to 50 and 100 mg PFOS/kg diet. Liver/body weight was significantly increased in females exposed to 2 mg PFOS/kg diet and in males exposed to 20 mg PFOS/kg diet. Female rats exposed to 100 mg PFOS/kg diet exhibited a significant increase in spleen weight relative to body weight; these changes lacked a histologic correlate and were not observed in males. While thymus weights relative to body weights were not affected, numbers of apoptotic lymphocytes rose in thymus with increasing dietary PFOS. There was a significant dose-related increase in total peripheral blood lymphocyte numbers in female but not male rats. In both genders the percentages of cells within lymphocyte subclasses were altered. There was a significant trend toward increasing T and T-helper (Th) cells and decreasing B cells with higher PFOS dose. Serum total immunoglobulin (Ig) G1 levels were significantly reduced in males exposed to 2 and 20 mg PFOS/kg diet. The ability of male and female rats to mount delayed-type hypersensitivity (DTH) responses to the T-cell-dependent antigen keyhole limpet hemocyanin (KLH) was not altered by PFOS. There was a significant trend toward elevated KLH-specific IgG in serum from male rats exposed to increasing levels of PFOS in diet. Splenic T- and B-cell proliferation in response to ex vivo mitogen exposure was unaffected by exposure to dietary PFOS. In conclusion, changes in immune parameters in rat did not manifest as functional alterations in response to immune challenge with KLH and may be secondary to hepatic-mediated effects of PFOS in this model.			●	●	●				●	-		B	B
1494	実験動物（免疫毒性）	Luster, M I; Portier, C; Pait, D G; Rosenthal, G J; Germolec, D R; Corsini, E; Blaylock, B L; Pollock, P; Kouchi, Y; Craig, W	Risk assessment in immunotoxicology	1993	Fundam Appl Toxicol. 1993 Jul;21(1):71-82. doi: 10.1006/faat.1993.1074.	We have reported on the design and content of a screening battery using a "tier" approach for detecting potential immunotoxic compounds in mice (Luster et al., Fundam. Appl. Toxicol., 10, 2-19, 1988). The data base generated from these studies, which consists of over 50 selected compounds, has been collected and analyzed in an attempt to improve future testing strategies and provide information to aid in developing future quantitative risk assessment for immunotoxicity. In a recent study it was shown that as few as two or three immune parameters were needed to predict immunotoxicants in mice (Luster et al., Fundam. Appl. Toxicol., 18, 200-210, 1992). In particular, enumeration of lymphocyte populations and quantitation of the T-dependent antibody response were particularly beneficial. Furthermore, commonly employed apical measures (e.g., leukocyte counts, lymphoid organ weights) were fairly insensitive. The present analyses focus on the use of this data base to develop statistical models that examine the qualitative and quantitative relationship(s) between the immune function and host resistance tests. The conclusion derived from these analyses are: (1) A good correlation exists between changes in the immune tests and altered host resistance in that there were no instances where host resistance was altered without affecting an immune test(s). However, in some instances immune changes occurred without corresponding changes in host resistance. (2) No single immune test could be identified which was fully predictive for altered host resistance, although most assays were relatively good indicators (i.e., > 70%). Several others, such as proliferative response to lipopolysaccharide and leukocyte counts, were found to be relatively poor indicators for host resistance changes. (3) The ability to resist infectious agent challenge is dependent upon the degrees of immunosuppression and the quantity of infectious agent administered. (4) Logistic and standard regression modeling using one extensive chemical data set from the immunosuppressive agent, cyclophosphamide, indicated that most immune function-host resistance relationships followed linear rather than linear-quadratic (threshold-like) models. For most of the relationships this could not be confirmed using a large chemical data set and, thus, a more mechanistically based approach for modeling will need to be developed. (5) Using this limited data set, methods were developed for modeling the precise quantitative relationships between changes in selected immune tests and host resistance tests.			●							-		D	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	情報抽出	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022					
1495	MOA（免疫毒性）	Midgett, Kristin; Peden-Adams, Margie M; Gilkeson, Gary S; Kamen, Diane L	In vitro evaluation of the effects of perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) on IL-2 production in human T-cells	2015	J Appl Toxicol. 2015 May;35(5):459-65. doi: 10.1002/jat.3037. Epub 2014 Jul 23.	Perfluorinated compounds, such as perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA), have been shown to alter various immune functions suggesting they are immunotoxic. This study assessed the effects of PFOS and PFOA on interleukin (IL)-2 production in the human Jurkat T-cell line and PFOS in healthy human primary T cells. Jurkat cells were stimulated with phytohemagglutinin (PHA)/phorbol myristate acetate (PMA), anti CD-3/anti CD-28, or anti CD-3, and dosed with 0, 0.05, 0.1, 0.5, 1, 5, 10, 50, 75, or 100 μg ml(-1) PFOS or 0, 0.005, 0.01, 0.05, 0.1, 0.5, 1, 5, or 10 μg ml(-1) PFOA. Jurkat cells stimulated with PHA/PMA or anti CD-3 exhibited decreased IL-2 production beginning at 50 μg PFOS ml(-1) and 5 μg PFOS ml(-1) respectively, but stimulation with anti-CD3/anti-CD28 resulted in no changes compared with the control. Addition of the PPAR-alpha antagonist GW6471 to PFOS-dosed cells stimulated with PHA/PMA resulted in decreases in IL-2 production starting at 50 μg PFOS ml(-1), which suggests PFOS affected T-cell IL-2 production via PPAR-alpha-independent mechanisms. Exposure to PFOA, PFOA + GW6471, or PFOS + PFOA in Jurkat cells resulted in no significant differences in IL-2 production. In vitro dosing studies using healthy primary human CD4+ T cells were consistent with the Jurkat results. These data demonstrated that PFOA did not impact IL-2 production, but PFOS suppressed IL-2 production in both a human cell line and human primary cells at dose levels within the high end of the human exposure range. A decrease in IL-2 production is characteristic of autoimmune diseases such as systemic lupus erythematosus and should be further investigated.			●							-			B	B
1496	実験動物（免疫毒性）	Mollenhauer, Meagan A M; Bradshaw, Sarah G; Fair, Patricia A; McGuinn, W David; Peden-Adams, Margie M	Effects of perfluorooctane sulfonate (PFOS) exposure on markers of inflammation in female B6C3F1 mice	2011	J Environ Sci Health A Tox Hazard Subst Environ Eng. 2011;46(2):97-108. doi: 10.1080/10934529.2011.532418.	Perfluorooctane sulfonate (PFOS; 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-1-octanesulfonic acid) has been reported to alter humoral immune functions, but inflammatory processes following PFOS exposure have not been fully characterized. Therefore, the current study, assessed TNF-α and IL-6 concentrations in serum and peritoneal lavage fluid, numbers of splenoctyes expressing intracellular TNF-α, IL-6, IL-10 or IL-1, and ex vivo TNF-α and IL-6 production by peritoneal macrophages following either in vivo or in vitro LPS exposure. Adult female B6C3F1 mice were exposed orally for 28 days to 0, 1, 3, or 300 mg PFOS/kg total administered dose [TAD] (e.g., 0, 0.0331, 0.0993 or 9.93 mg/kg/day). Body and spleen masses were significantly reduced in the highest PFOS treatment group compared to the control group, whereas liver mass was significantly increased. Serum TNF-α levels were significantly decreased following exposure to 1 mg PFOS/kg TAD as compared to controls, while serum IL-6 levels were increased. IL-6 concentrations in peritoneal lavage fluid decreased with increasing dose. PFOS treatment did not alter numbers of splenocytes expressing intracellular levels of TNF-α, IL-10 or IL-1. Numbers of splenocytes expressing intracellular levels of IL-6 were significantly decreased in the 3 mg/kg treatment as compared to controls. Overall, these data suggest that PFOS exposure can alter some inflammatory processes, which could potentially lead to misdirected inflammatory responses.			●		●					-		1	A	B
1497	実験動物（免疫毒性）	Pachkowski, Brian; Post, Gloria B; Stern, Alan H	The derivation of a Reference Dose (RfD) for perfluorooctane sulfonate (PFOS) based on immune suppression	2019	Environ Res. 2019 Apr;171:452-469. doi: 10.1016/j.envres.2018.08.004. Epub 2018 Aug 8.	Exposure to perfluorooctane sulfonate (PFOS) is ubiquitous in populations and environments worldwide. Its long half-life in humans, indefinite persistence in the environment, and awareness of its widespread presence in drinking water make the human health assessment of PFOS a priority. While developmental, endocrine, and hepatic effects, and increased serum cholesterol are among the outcomes resulting from PFOS exposure, immunosuppression has also consistently emerged as an adverse effect. An in-depth review of the relevant scientific literature on the toxicology of PFOS has identified immunosuppression as a sensitive endpoint for PFOS toxicity. Here, we focus specifically on that endpoint and provide a detailed derivation of a Reference Dose (RfD) of 1.8 × 10(-6) mg/kg/day for chronic human exposure to PFOS. This RfD is based on decreased plaque-forming cell (PFC) response in mice, an endpoint that reflects suppression of the immune response to a foreign antigen. We additionally identify two endpoints in the epidemiology literature, decreased vaccine response and increased incidence of childhood infections, that are associated with PFOS exposure and that are consistent with and support the decreased PFC response endpoint from animal studies. We provide a weight of evidence analysis integrating the evidence from animal and epidemiology endpoints. Finally, we compare this RfD to the PFOS RfD derived by the United States Environmental Protection Agency (USEPA) Office of Water based on a developmental endpoint. Based on this comparison, and given our assessment, the USEPA RfD does not provide sufficient protection against the adverse health effects of PFOS. The RfD derived herein is intended to be public health protective and appropriately minimizes PFOS exposure based on available evidence.			●						●	-			A	B
1498	ヒト（免疫毒性）	Pennings, Jeroen L A; Jennen, Danyel G J; Nygaard, Unni C; Namork, Ellen; Haug, Line S; van Loveren, Henk; Granum, Berit	Cord blood gene expression supports that prenatal exposure to perfluoroalkyl substances causes depressed immune functionality in early childhood	2016	J Immunotoxicol. 2016;13(2):173-80. doi: 10.3109/1547691X.2015.1029147. Epub 2015 Mar 27.	Perfluoroalkyl and polyfluoroalkyl substances (PFAS) are a class of synthetic compounds that have widespread use in consumer and industrial applications. PFAS are considered environmental pollutants that have various toxic properties, including effects on the immune system. Recent human studies indicate that prenatal exposure to PFAS leads to suppressed immune responses in early childhood. In this study, data from the Norwegian BraMat cohort was used to investigate transcriptomics profiles in neonatal cord blood and their association with maternal PFAS exposure, anti-rubella antibody levels at 3 years of age and the number of common cold episodes until 3 years. Genes associated with PFAS exposure showed enrichment for immunological and developmental functions. The analyses identified a toxicogenomics profile of 52 PFAS exposure-associated genes that were in common with genes associated with rubella titers and/or common cold episodes. This gene set contains several immunomodulatory genes (CYTL1, IL27) as well as other immune-associated genes (e.g. EMR4P, SHC4, ADORA2A). In addition, this study identified PPARD as a PFAS toxicogenomics marker. These markers can serve as the basis for further mechanistic or epidemiological studies. This study provides a transcriptomics connection between prenatal PFAS exposure and impaired immune function in early childhood and supports current views on PPAR- and NF-κB-mediated modes of action. The findings add to the available evidence that PFAS exposure is immunotoxic in humans and support regulatory policies to phase out these substances.			●							-		1	D	A
1499	実験動物（免疫毒性）	Qazi, Mousumi Rahman; Nelson, B Dean; Depierre, Joseph W; Abedi-Valugerdi, Manuchehr	28-Day dietary exposure of mice to a low total dose (7 mg/kg) of perfluorooctanesulfonate (PFOS) alters neither the cellular compositions of the thymus and spleen nor humoral immune responses: does the route of administration play a pivotal role in PFOS-induced immunotoxicity	2010	Toxicology. 2010 Jan 12;267(1-3):132-9. doi: 10.1016/j.tox.2009.10.035. Epub 2009 Nov 10.	Short-term exposure of mice to high doses of perfluorooctanesulfonate (PFOS), an ubiquitous and highly persistent environmental contaminant, induces various metabolic changes and toxic effects, including immunotoxicity. However, extrapolation of these findings to the long-term, low-dose exposures to which humans are subject is highly problematic. In this connection, recent studies have concluded that sub-chronic (28-day) exposure of mice by oral gavage to doses of PFOS that result in serum levels comparable to those found in general human populations suppress adaptive immunity. Because of the potential impact of these findings on environmental research and monitoring, we have examined here whether sub-chronic dietary exposure (a major route of human exposure) to a similarly low-dose of PFOS also suppress adaptive immune responses. Dietary treatment of male B6C3F1 mice for 28 days with a dose of PFOS that resulted in a serum concentration of 11mug/ml (ppm) significantly reduced body weight gain and increased liver mass. However, this treatment did not alter the cellular compositions of the thymus and spleen; the number of splenic cells secreting IgM antibodies against sheep red blood cell (SRBC); serum levels of IgM and IgG antibodies specifically towards SRBC; or circulating levels of IgM antibodies against the T-cell-independent antigen trinitrophenyl conjugated to lipopolysaccharide (TNP-LPS). These findings indicate that such sub-chronic dietary exposure of mice to PFOS resulting in serum levels approximately 8-85-fold greater than those observed in occupationally exposed individuals does not exert adverse effects on adaptive immunity.			●	●	●					-			B	B
1500	実験動物（免疫毒性）	Qazi, Mousumi Rahman; Nelson, B Dean; DePierre, Joseph W; Abedi-Valugerdi, Manuchehr	High-dose dietary exposure of mice to perfluorooctanoate or perfluorooctane sulfonate exerts toxic effects on myeloid and B-lymphoid cells in the bone marrow and these effects are partially dependent on reduced food consumption	2012	Food Chem Toxicol. 2012 Sep;50(9):2955-63. doi: 10.1016/j.fct.2012.06.023. Epub 2012 Jun 23.	It is well established that exposure of mice to perfluorooctanoate (PFOA) or perfluorooctane sulfonate (PFOS) exerts adverse effects on the thymus and spleen. Here, we characterize the effects of a 10-day dietary treatment with these compounds (0.001-0.02%, w/w) on the bone marrow (BM) of mice. At a dose of 0.02%, both compounds reduced food consumption and caused atrophy of the thymus and spleen. At this same dose, histopathological and flow cytometric analysis revealed that (i) the total numbers of BM as well as the numbers of myeloid, pro/pre B, immature B and early mature B cells were all reduced significantly; and (ii) these adverse effects were reversed either partially or completely 10days after withdrawal of these compounds. At the lower dose of 0.002%, only PFOA reduced the B-lymphoid cell population. Finally, mice fed an amount of diet equivalent to that consumed by the animals exposed to 0.02% PFOA also exhibited atrophy of the thymus and spleen, and a reduction in the number of B-lymphoid population, without affecting myeloid cells. Thus, in mice, immunotoxic doses of PFOA or PFOS induce adverse effects on the myeloid and B-lymphoid cells in the BM, in part as a consequence of reduced food consumption.			●	●					●	-			B	B
1501	実験動物（免疫毒性）	Ryu, Min H; Jha, Aruni; Ojo, Oluwaseun O; Mahood, Thomas H; Basu, Sujata; Detillieux, Karen A; Nikoobakht, Neda; Wong, Charles S; Loewen, Mark; Becker, Allan B; Halayko, Andrew J	Chronic exposure to perfluorinated compounds: impact on airway hyperresponsiveness and inflammation	2014	Am J Physiol Lung Cell Mol Physiol. 2014 Nov 15;307(10):L765-74. doi: 10.1152/ajplung.00100.2014. Epub 2014 Sep 12.	Emerging epidemiological evidence reveals a link between lung disease and exposure to indoor pollutants such as perfluorinated compounds (PFCs). PFC exposure during critical developmental stages may increase asthma susceptibility. Thus, in a murine model, we tested the hypothesis that early life and continued exposure to two ubiquitous household PFCs, perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS), can induce lung dysfunction that exacerbates allergen-induced airway hyperresponsiveness (AHR) and inflammation. Balb/c mice were exposed to PFOA or PFOS (4 mg/kg chow) from gestation day 2 to 12 wk of age by feeding pregnant and nursing dams, and weaned pups. Some pups were also sensitized and challenged with ovalbumin (OVA). We assessed lung function and inflammatory cell and cytokine expression in the lung and examined bronchial goblet cell number. PFOA, but not PFOS, without the OVA sensitization/challenge induced AHR concomitant with a 25-fold increase of lung macrophages. PFOA exposure did not affect OVA-induced lung inflammatory cell number. In contrast, PFOS exposure inhibited OVA-induced lung inflammation, decreasing total cell number in lung lavage by 68.7%. Interferon-γ mRNA in the lung was elevated in all PFC-exposed groups. Despite these effects, neither PFOA nor PFOS affected OVA-induced AHR. Our data do not reveal PFOA or PFOS exposure as a risk factor for more severe allergic asthma-like symptoms, but PFOA alone can induce airway inflammation and alter airway function.			●	●						-			B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献ラン①抽出	文献ラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1502	実験動物（免疫毒性）	Suo, Caixia; Fan, Zhiqin; Zhou, Liang; Qiu, Ju	Perfluorooctane sulfonate affects intestinal immunity against bacterial infection	2017	Sci Rep. 2017 Jul 12;7(1):5166. doi: 10.1038/s41598-017-04091-z.	Perfluorooctane sulfonate (PFOS) is an environmental contaminant that has been manufactured to be used as surfactants and repellents in industry. Due to long half-life for clearance and degradation, PFOS is accumulative in human body and has potential threat to human health. Previous studies have shown the development and function of immune cells can be affected by PFOS. Although PFOS has a high chance of being absorbed through the oral route, whether and how PFOS affects immune cells in the gut is unknown. Using mouse model of Citrobacter rodentium infection, we investigated the role of PFOS on intestinal immunity. We found at early phase of the infection, PFOS inhibited the expansion of the pathogen by promoting IL-22 production from the group 3 innate lymphoid cell (ILC3) in an aryl hydrocarbon receptor dependent manner. Nevertheless, persistent PFOS treatment in mice finally led to a failure to clear the pathogen completely. At late phase of infection, enhanced bacterial counts in PFOS treated mice were accompanied by increased inflammatory cytokines, reduced mucin production and dysbiosis, featured by decreased level of Lactobacillus casei, Lactobacillus johnsonii and increased E. coli. Our study reveals a deleterious consequence in intestinal bacterial infection caused by PFOS accumulation.			●							-		B	B
1503	in vitro（免疫毒性）	Van Loveren, H; Van Amsterdam, J G; Vandebriel, R J; Kimman, T G; Rümke, H C; Steerenberg, P S; Vos, J G	Vaccine-induced antibody responses as parameters of the influence of endogenous and environmental factors	2001	Environ Health Perspect. 2001 Aug;109(8):757-64. doi: 10.1289/ehp.01109757.	In laboratory animals, an adequate way to assess effects of environmental exposures on the immune system is to study effects on antigen-specific immune responses, such as after sensitization to T-cell-dependent antigens. This probably also applies to testing effects in the human population. It has thus been suggested that antibody responses to vaccination might be useful in this context. Vaccination responses may be influenced by a variety of factors other than environmental ones. One factor is the vaccine itself; a second is the vaccination procedure used. In addition, the intrinsic capacity of the recipient to respond to a vaccine, which is determined by sex, genetic factors, and age, is important. Psychological stress, nutrition, and (infectious) diseases are also likely to have an impact. We reviewed the literature on vaccine response. With regard to exogenous factors, there is good evidence that smoking, diet, psychological stress, and certain infectious diseases affect vaccination titers, although it is difficult to determine to what extent. Genetic factors render certain individuals nonresponsive to vaccination. In general, in epidemiologic studies of adverse effects of exposure to agents in the environment in which vaccination titers are used, these additional factors need to be taken into consideration. Provided that these factors are corrected for, a study that shows an association of exposure to a given agent with diminished vaccination responses may indicate suboptimal function of the immune system and clinically relevant diminished immune response. It is quite unlikely that environmental exposures that affect responses to vaccination may in fact abrogate protection to the specific pathogen for which vaccination was performed. Only in those cases where individuals have a poor response to the vaccine may exogenous factors perhaps have a clinically significant influence on resistance to the specific pathogen. An exposure-associated inhibition of a vaccination response may, however, signify a decreased host resistance to pathogens against which no vaccination had been performed.			●							-		D	C
1504	実験動物（免疫毒性）	Vetvicka, V.; Vetvickova, J.	Reversal of perfluorooctanesulfonate-induced immunotoxicity by a glucan resveratrol-vitamin C combination	2013	Oriental Pharmacy and Experimental Medicine, 13, 77–84.	Perfluorinated compounds (PFCs) perfluoroctanic acid (PFOA) and perfluooctane sulphonic acid (PFOS) are environmentally widespread bioaccumulative chemicals known to induce profound effects on the immune system. In this study, two types of PFC, i.e., PFOS and PFOA, were administered orally (daily) a dose of 20 mg/kg/d. After exposure, all mice exhibited significant immunosuppressive effects upon both cellular (phagocytosis and NK cell activity) and humoral (antibody response) branches of their immune responses. The mice were then fed with a 4 mg/kg/d dose of a combination of resveratrol-glucan-vitamin C (RVB 300). The results showed that treatment with PFCs and RVB 300 resulted in significantly lower level of immunotoxic effects from PFCs. These outcomes suggest to us that RVB 300 can potentially be successfully used as a natural remedy against immunotoxicities induced by low-level exposure(s) to perfluorinated compounds.			●	●					●	-		B	B
1505	実験動物（免疫毒性）	Wang, Yu; Wang, Ling; Liang, Yong; Qiu, Wenhong; Zhang, Jie; Zhou, Qunfang; Jiang, Guibin	Modulation of dietary fat on the toxicological effects in thymus and spleen in BALB/c mice exposed to perfluorooctane sulfonate	2011	Toxicol Lett. 2011 Jul 28;204(2-3):174-82. doi: 10.1016/j.toxlet.2011.04.029. Epub 2011 May 6.	Perfluorooctane sulfonate (PFOS) can cause atrophy of the immune organs in rodents, but the mechanism underlying this action is not completely understood. In this study, BALB/c mice were fed a regular (RD) or high-fat diet (HFD). They were then exposed to PFOS (0, 5, and 20mg/kg/day) for 14 days. In the RD-exposure group, body weight significantly decreased and the immune organs showed considerable atrophy. Histopathological analyses showed that the corticomedullary junction of the thymus was indistinguishable, and sinus expansion in the spleen was observed. Transmission electron microscopy (TEM) results showed that lipofuscin granules and vacuoles appeared in the thymus and spleen. Increased apoptosis of thymocytes was observed. In the HFD group, all of these phenomena were not eliminated. More serious atrophy was seen in the immune organs under TEM. Even more adipocytes were in the lobules of the thymus in the HFD 20mg/kg/day PFOS groups. Expression of the proliferator-activated receptor-alpha and interleukin-1 beta were upregulated in the thymus and spleen in all exposure groups. These results suggest that PFOS may indirectly attack the immune organs by interfering with lipid metabolism, leading to co-senescence of the thymus and spleen. These data may aid understanding of how PFOS affects the immune system.			●							-		B	B
1506	MOA（免疫毒性）	Zarei, Mohammad Hadi; Hosseini Shirazi, Seyed Farshad; Aghvami, Marjan; Pourahmad, Jalal	Perfluorooctanesulfonate (PFOS) Induces Apoptosis Signaling and Proteolysis in Human Lymphocytes through ROS Mediated Mitochondrial Dysfunction and Lysosomal Membrane Labialization	2018	Iran J Pharm Res. 2018 Summer;17(3):995-1007.	Perfluorinated compounds (PFCs) such as perfluorooctanesulfonate (PFOS) are stable chemicals that accumulate in biological matrix. Toxicity of these compounds including immunotoxicity has been demonstrated in experimental models and wildlife. Although limited number of studies examined the effects of PFOS on human lymphocytes but so far no research has investigated the complete mechanisms of PFOS cytotoxicity toward human lymphocytes. The main goal of this investigation was to find out the mechanisms underlying the cytotoxic effect of PFOS toward human lymphocytes using accelerated cytotoxicity mechanisms screening (ACMS) technique. Human lymphocytes were isolated from blood of healthy donors using Ficoll-paquePLUS standard method. Cell viability was determined following 12 h of incubation of human lymphocytes with 100-500 μM PFOS. Our results showed that IC(50) concentration (163.5 μM) of PFOS reduced viability of human lymphocytes approximately 50% via increased ROS formation, lipid peroxidation, glutathione depletion and damage to cell sub organelles such as mitochondria and lysosomes. Besides, in this study we demonstrated involvement of cellular proteolysis and activation of caspase-3 in PFOS induced lymphocyte cytotoxicity. We finally concluded that at environmentally related concentration, PFOS can induce toxic effect toward human lymphocytes through induction of oxidative stress and damage to cell sub organelles.			●							-		B	B
1507	実験動物（免疫毒性）	Zhang, Ying-Hua; Wang, Jing; Dong, Guang-Hui; Liu, Miao-Miao; Wang, Da; Zheng, Li; Jin, Yi-He	Mechanism of perfluorooctanesulfonate (PFOS)-induced apoptosis in the immunocyte	2013	J Immunotoxicol. 2013 Jan-Mar;10(1):49-58. doi: 10.3109/1547691X.2012.691123. Epub 2012 Sep 7.	As a new type of persistent organic pollutant, perfluorooctane sulfonate (PFOS) has raised great concern in recent years due to its ubiquitous distribution in the general environment and its long elimination half-life in humans. PFOS has toxic and carcinogenic effects in animals and humans, but the effects of PFOS on apoptosis are still not clear. The present study aimed to determine the mode of cell death and its mechanism in splenocytes and thymocytes from adult male C57BL/6 mice administered 0, 1, 5, or 10 mg PFOS/kg/day by gavage daily for 7 days. The results showed that more apoptotic cells were present in PFOS-treated mice than in control mice. PFOS induced production of reactive oxygen species (ROS), dissipation of mitochondria membrane potential, and apoptosis of splenocytes and thymocytes. Moreover, activities of superoxide dismutase, catalase, and glutathione reductase were increased, whereas activities of glutathione-S-transferase and glutathione peroxidase were decreased, in splenocytes. Glutathione contents were reduced as well. Differential expressions of proteins such as p53, Bax, caspase-3, and caspase-9 were significantly up-regulated in PFOS-exposed hosts, whereas Bcl-2 expression was significantly down-regulated. One possible mechanism for the findings here was that PFOS could overwhelm homeostasis of anti-oxidative systems, boost ROS generation, impact on mitochondria, and affect protein expression of apoptotic regulators, the latter of which resulted in initiation of the apoptosis program. Results from this study may provide a new insight into the potential adverse effects of PFOS exposure on humans, at the cellular level.			●							-		B	B
1508	実験動物（免疫毒性）	Zheng, Li; Dong, Guang-Hui; Zhang, Ying-Hua; Liang, Zai-Fu; Jin, Yi-He; He, Qin-Cheng	Type 1 and Type 2 cytokines imbalance in adult male C57BL/6 mice following a 7-day oral exposure to perfluorooctanesulfonate (PFOS)	2011	J Immunotoxicol. 2011 Jan-Mar;8(1):30-8. doi: 10.3109/1547691X.2010.537287.	Previous studies indicate that exposure to perfluorooctanesulfonate (PFOS), a ubiquitous and highly persistent environmental contaminant induces immunotoxicity in mice. However, clear mechanisms to explain any PFOS-induced immunotoxicity are still unknown. The study here sought to examine the ability of PFOS to potentially perturb T-helper (T(H))-1 and -2 cell cytokine secreting activities, as well as to cause shifts in antibody isotype levels, as possible mechanisms involved in PFOS-induced immunotoxicity. Adult male C57BL/6 mice were given by gavage 0, 5, or 20 mg PFOS/kg/d for 7 days. One day after the final exposure, spleens from these hosts were isolated and used for analyses of the ex vivo production of T(H)1-type (interleukin-2 (IL-2), interferon-γ (IFNγ), T(H)2-type (IL-4), and IL-10 cytokines by isolated splenocytes. In addition, serum was isolated from these mice in order to assess their levels of immunoglobulin M (IgM) and IgG antibodies. In all studies, levels of the cytokines of the antibodies were quantified via enzyme-linked immunosorbent assay or enzyme-linked immunosorbent spot. The results here showed that IL-2 and IFNγ formation was reduced, but that IL-4 production increased by the 5 and 20 mg PFOS/kg/d treatments. Serum IgM levels decreased significantly (in dose-related manner) as a result of the PFOS exposures; serum IgG levels increased markedly with 5 mg PFOS/kg/d, but decreased slightly with the 20 mg PFOS/kg/d regimens PFOS exposure increased serum corticosterone levels in a dose-dependent manner. These results indicated that, after a high-dose short-term exposure to PFOS, a host's immune state is likely to be characterized by a shift toward a more T(H)2-like state that, in turn, may lead to suppression of their cellular response and enhancement of their humoral response.			●						●	-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①A	文献クラン②B
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1509	実験動物（免疫毒性）	Fairley, Kimberly J; Purdy, Rich; Kearns, Shaun; Anderson, Stacey E; Meade, B J	Exposure to the immunosuppressant, perfluorooctanoic acid, enhances the murine IgE and airway hyperreactivity response to ovalbumin	2007	Toxicol Sci. 2007 Jun;97(2):375-83. doi: 10.1093/toxsci/kfm053. Epub 2007 Mar 15.	These studies were conducted to investigate the role of dermal exposure to perfluorooctanoic acid (PFOA), a known immunosuppressant, on the hypersensitivity response to ovalbumin (OVA) in a murine model of asthma. PFOA has had widespread use as a carpet and fabric protectant. BALB/c mice were exposed dermally, on the dorsal surface of each ear, to concentrations of PFOA ranging from 0.01 to 1.5% (applied dose 0.25-50 mg/kg) for 4 days. In hypersensitivity studies, mice were also ip injected with 7.5 microg OVA and 2 mg alum on days 1 and 10 and in some studies challenged with 250 microg OVA by pharyngeal aspiration on days 17 and 26. Following exposure to PFOA, an increase in liver weights and a decrease in thymus and spleen weights and cellularities were observed. Similar immunomodulatory trends were demonstrated in mice coadministered PFOA and OVA. Compared to the OVA alone-exposed animals, an increase in total IgE was demonstrated when mice were coexposed to OVA and concentrations of PFOA ranging from 0.75 to 1.5%, while the OVA-specific IgE response peaked with 0.75% PFOA coexposure (p < or = 0.05). OVA-specific airway hyperreactivity was increased in the 1.0% PFOA coexposed group (p < or = 0.05), with an increased pleiotropic cell response characterized by eosinophilia and mucin production, in animals coexposed to concentrations of PFOA up to 1.0%, as compared to the OVA alone-exposed animals. In a murine model, PFOA was demonstrated to be immunotoxic following dermal exposure, with an enhancement of the hypersensitivity response to OVA, suggesting that PFOA exposure may augment the IgE response to environmental allergens.				●		●				-	1	A	B
1510	実験動物（免疫毒性）	Fang, Xuemei; Feng, Yixing; Wang, Jianshe; Dai, Jiayin	Perfluorononanoic acid-induced apoptosis in rat spleen involves oxidative stress and the activation of caspase-independent death pathway	2010	Toxicology. 2010 Jan 12;267(1-3):54-9. doi: 10.1016/j.tox.2009.10.020. Epub 2009 Oct 28.	Perfluoroalkyl acid (PFAA)-induced apoptosis has been reported in many cell types. However, minimal information on its mode of action is available. This study explored the possible involvement of apoptotic signaling pathways in a nine-carbon-chain length PFAA-perfluorononanoic acid (PFNA)-induced splenocyte apoptosis. After a 14-day exposure to PFNA, rat spleens showed dose-dependent levels of apoptosis. The production of pro-inflammatory and anti-inflammatory cytokines was significantly increased and decreased, respectively. However, protein levels of tumor necrosis factor receptor 1 (TNFR1), fas-associated protein with death domain (FADD), caspase 8 and caspase 3, which are involved in inflammation-related and caspase-dependent apoptosis, were discordant. Peroxisome proliferator-activated receptors alpha (PPARalpha) and PPARgamma genes expression was up-regulated in rats treated with 3 or 5 mg/kg/day of PFNA, and the level of hydrogen peroxide (H2O2) increased concurrently in rats treated with the highest dose. Moreover, superoxide dismutase (SOD) activity and Bcl-2 protein levels were dramatically decreased in spleens after treatment with 3 and 5 mg/kg/day of PFNA. However, protein levels of Bax were unchanged. Apoptosis-inducing factor (AIF), an initiator of caspase-independent apoptosis, was significantly increased in all PFNA-dosed rats. Thus, oxidative stress and the activation of a caspase-independent apoptotic signaling pathway contributed to PFNA-induced apoptosis in rat splenocytes.				●						-		B	B
1511	実験動物（免疫毒性）	Hu, Qing; Strynar, Mark J; DeWitt, Jamie C	Are developmentally exposed C57BL/6 mice insensitive to suppression of TDAR by PFOA?	2010	J Immunotoxicol. 2010 Oct-Dec;7(4):344-9. doi: 10.3109/1547691X.2010.520045. Epub 2010 Oct 18.	Perfluorooctanoic acid (PFOA) is an environmentally persistent fluorinated compound that is present in biological samples worldwide and associated with multisystem toxicity in laboratory animal models. Several studies have reported suppression of T-cell-dependent antibody responses (TDAR) in adult rodent models after 15 or 28 days of exposure. A related compound, perfluorooctane sulfonate (PFOS), was reported to suppress TDAR in developmentally exposed mice. The developmental effects of PFOA exposure on TDAR have not been explored; therefore, the objective of our study was to determine if TDAR suppression would occur in developmentally exposed mice. Pregnant C57BL/6 mice were given 0, 0.5, or 1 mg PFOA/kg body weight (BW) in drinking water from gestation day (GD) 6 to GD17. At postnatal day (PND) 2, litters/dam were reduced to three males and three females. On PND21, female offspring were weaned and separated and on PND43, they were intravenously immunized with sheep red blood cells. Serum for evaluation of IgM titers and PFOA concentrations was collected 5 days later. Booster immunizations were given 14 days later; serum for evaluation of IgG titers and PFOA concentrations was collected 5 days later. Litter weights were statistically decreased by 10% in the 1 mg/kg group relative to controls, but liver weights, lymphoid organ weights, and TDAR did not differ in female offspring by dose. Mean PFOA serum concentrations were 122 ng/mL (0.5 mg/kg) and 183 ng/mL (1 mg/kg) and <1 ng/mL for controls. PFOA serum concentrations in offspring were 400-fold lower than serum concentrations reported to suppress TDAR in adults; however, mice exposed during development did not survive doses higher than 1 mg/kg. Therefore, although TDAR in adult mice is sensitive to PFOA exposure, the doses and exposure scenario of this study did not induce developmental immunotoxicity (DIT). C57BL/6 mice are likely more sensitive to the overt developmental toxicity of PFOA than to potential DIT.				●						-		B	B
1512	実験動物（免疫毒性）	NTP	NTP Monograph on immunotoxicity associated with exposure to perfluorooctanoic acid (PFOA) or perfluorooctane sulfonate (PFOS)	2016	Available at https://ntp.niehs.nih.gov/ntp/ohat/pfoa_pfos/pfoa_pfosmonograph_508.pdf	Although emissions of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) have been dramatically reduced, the persistence and bioaccumulation of these chemicals result in detectable levels in the U.S. population. Despite declining emissions, there is continued widespread exposure to both chemicals and a number of studies have reported potential PFOA- and PFOS-associated immunotoxicity in both humans and non-human animals. The NTP conducted a systematic review to evaluate the evidence on exposure to PFOS or PFOA and immune-related health effects to determine whether exposure to either chemical is associated with immunotoxicity for humans. The literature search and screening process identified 33 human studies, 93 animal studies, and 27 in vitro/mechanistic studies relevant for addressing the objective. The health effects data for PFOA and PFOS were considered separately in developing hazard identification conclusions. Conclusions for each chemical were reached by integrating evidence from human and animal studies with consideration of any mechanistic data. The NTP concludes that PFOA is presumed to be an immune hazard to humans based on a high level of evidence that PFOA suppressed the antibody response from animal studies and a moderate level of evidence from studies in humans. Although the strongest evidence for an effect of PFOA on the immune system is for suppression of the antibody response, there is additional, although weaker, evidence that is primarily from epidemiological studies that PFOA reduced infectious disease resistance, increased hypersensitivity-related outcomes, and increased autoimmune disease incidence. The evidence indicating that PFOA affects multiple aspects of the immune system supports the overall conclusion that PFOA alters immune function in humans. However, the mechanism(s) of PFOA-associated immunotoxicity is not clearly understood and effects on diverse endpoints such as suppression of the antibody response and increased hypersensitivity may be unrelated. The NTP concludes that PFOS is presumed to be an immune hazard to humans based on a high level of evidence that PFOS suppressed the antibody response from animal studies and a moderate level of evidence from studies in humans. Although the strongest evidence for an effect of PFOS on the immune system is for suppression of the antibody response, there is additional, although weaker, evidence that is primarily from studies in experimental animals that PFOS suppresses disease resistance and natural killer (NK) cell activity. The evidence indicating that PFOS suppresses multiple aspects of the immune system supports the overall conclusion that PFOS alters immune function in humans. Although the mechanism(s) of PFOS-associated				●	●	●			●	評価書		B	B
1513	実験動物（免疫毒性）	Yang, Qian; Abedi-Valugerdi, Manuchehr; Xie, Yi; Zhao, Xiao-Yan; Möller, Göran; Nelson, B Dean; DePierre, Joseph W	Potent suppression of the adaptive immune response in mice upon dietary exposure to the potent peroxisome proliferator, perfluorooctanoic acid	2002	Int Immunopharmacol. 2002 Feb;2(2-3):389-97. doi: 10.1016/s1567-5769(01)00164-3.	In a previous investigation, we demonstrated that severe thymus and spleen atrophy occurs in mice upon dietary exposure to several potent peroxisome proliferators (PPs). In the present investigation, the effects of the potent PP perfluorooctanoic acid (PFOA) on the adaptive immunity of mice was evaluated both in vivo and ex vivo. The in vivo immune response examined involved immunization of mice with horse red blood cells (HRBCs), displaying T-cell-dependent antigens after pre-treatment with a PFOA-containing diet for 10 days. Subsequent quantitation of the primary humoral response was performed employing both the plaque-forming cell (PFC) assay and determination of the antibody titer by ELISA. The results clearly demonstrate that oral administration of PFOA prevents both the increases in plaque formations by anti-IgM and -IgG and in serum levels of IgM and IgG normally evoked by such immunization. Ex vivo spleen cells proliferation (assayed as incorporation of 3H-thymidine) in response to both T- and B-cell activators was attenuated by dietary treatment with PFOA, although the analogous in vitro treatment of mouse spleen cells with this same compound had no such effects. Thus, the relatively metabolically inert PP PFOA may exert adaptive immunosuppression in mice by an indirect mechanism. The possible relevance of this immunosuppression to the alterations in plasma lipids caused by PPs is discussed.				●						-		B	B
1514	MOA（免疫毒性）	Collier, RJ.	Diphtheria toxin: mode of action and structure	1975	Bacteriological Reviews, 39: 54-85. doi: 10.1128/br.39.1.54-85.1975.	No abstract available		●							-		D	D
1515	実験動物（免疫毒性）	Dong, Guang-Hui; Zhang, Ying-Hua; Zheng, Li; Liang, Zai-Fu; Jin, Yi-He; He, Qin-Cheng	Subchronic effects of perfluorooctanesulfonate exposure on inflammation in adult male C57BL/6 mice	2012	Environ Toxicol. 2012 May;27(5):285-96. doi: 10.1002/tox.20642. Epub 2010 Aug 24.	Previous studies indicate that exposure to perfluorooctanesulfonate (PFOS), a ubiquitous and highly persistent environmental contaminant, induces immunotoxicity in mice. However, few studies have specifically assessed the effects of PFOS on inflammation. This study utilized a standard 60-day oral exposure period to assess the effects of PFOS on the response of inflammatory cytokines [tumor necrosis factor α (TNF-α), interleukin-1 β (IL-1 β), and interleukin-6 (IL-6)]. Adult male C57BL/6 mice were dosed daily by oral gavage with PFOS at 0, 0.0083, 0.0167, 0.0833, 0.4167, 0.8333 or 2.0833 mg/kg/day to yield a targeted Total Administered Dose (TAD) over 60 days of 0, 0.5, 1, 5, 25, 50, or 125 mg PFOS/kg, respectively. The percentage of peritoneal macrophages (CD11b+ cells) was significantly increased at concentrations ≥ 1 mg PFOS/kg TAD in a dose-dependent manner. Ex vivo IL-1β production by peritoneal macrophages was elevated substantially at concentrations of ≥ 5 mg PFOS/kg TAD. Moreover, PFOS exposure markedly enhanced the ex vivo production of TNF-α, IL-1β and IL-6 by peritoneal and splenic macrophages when stimulated either in vitro or in vivo with lipopolysaccharide (LPS). The serum levels of these inflammatory cytokines observed in response to in vivo stimulation with LPS were elevated substantially by exposure to PFOS. PFOS exposure elevated the expression of pro-inflammatory cytokines TNF-α, IL-1β, IL-6, and proto-oncogene, c-myc, in the spleen. These data suggest that exposure to PFOS modulates the inflammatory response, and further research is needed to determine the mechanism of action.					●					-	1	A	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①抽出	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1516	実験動物（発達神経毒性）	Chang, S. C.; Ehresman, D. J.; Bjork, J. A.; Wallace, K. B.; Parker, G. A.; Stump, D. G.; Butenhoff, J. L.	Gestational and lactational exposure to potassium perfluorooctanesulfonate (K+PFOS) in rats: toxicokinetics, thyroid hormone status, and related gene expression	2009	Reprod Toxicol. 2009 Jun;27(3-4):387-399. doi: 10.1016/j.reprotox.2009.01.005. Epub 2009 Jan 21.	Perfluorooctanesulfonate (PFOS), a persistent and accumulative compound, is widely distributed in humans and wildlife. Human exposure can occur early in development, as evidenced by the detection of PFOS in umbilical cord blood and breast milk. As part of a developmental neurotoxicology study for which developmental endpoints, including those related to the developing nervous system, have been reported separately, groups of 25 pregnant Sprague Dawley rats were given daily oral doses of either vehicle control or potassium PFOS (K(+)PFOS) at 0.1, 0.3, and 1.0mg/kg-d from gestation day (GD) 0 (day positive for mating) through postnatal day (PND) 20 An additional 10 pregnant females per treatment group were treated through GD 19 and sacrificed on GD 20 in order to obtain maternal and fetal serum and tissue samples at the end of gestation. The present paper reports the results of samples of serum, liver, brain, and thyroid glands taken at various times to evaluate: -1 serum, liver, and brain PFOS concentrations by LC-MS/MS to establish the relationship between PFOS concentrations and study outcomes; -2 serum thyrotropin (TSH) concentrations by RIA; -3 thyroid follicular cell proliferation index by Ki-67 immunohistochemical staining; -4 thyroid follicle epithelial cell height and colloidal area by histomorphometric analysis; 5 selected liver mRNA transcripts by quantitative RT-PCR. PFOS concentrations in dam and pup serum, liver, and brain increased across treatment groups in approximate proportion to the proportional increases in maternal K(+)PFOS dose, and sex differences in PFOS concentrations were not apparent in pups on PND 21 In pups from K(+)PFOS maternal dose groups on PND 72, serum PFOS had decreased to about 3 and 0.11 of PND 21 concentrations in males and females, respectively, and liver PFOS had decreased to about 0.17 of PND 21 concentrations in both sexes. Liver PFOS concentrations were approximately 0.6-0.8 times serum PFOS in GD 20 fetuses, and increased to about 44596 times serum concentrations on PND 4 and 21 GD 20 fetal and PND 4 pup brain PFOS concentrations were approximately 0.33 of the corresponding serum concentrations, dropping to approximately 0.1 by PND 21, in contrast to dam brain PFOS concentrations, which were approximately 4-9% of serum PFOS concentrations. Compared to controls, Cyp2b2 mRNA was increased (2.8-fold) in the 1.0mg/kg-d treatment-group dams on GD 20 In male pups on PND 21, Cyp4A1, ACoA, and Cyp2b2 were increased 2.1-, 1.5-, and 1.8-fold, respectively, and Cyp7A1 was decreased 3.5-fold. Serum TSH and thyroid follicular morphology	●	●		●	●		●		●	-		1	B	A
1517	実験動物（生殖発生毒性）	Cook, J. C.; Murray, S. M.; Frame, S. R.; Hurtt, M. E.	Induction of Leydig cell adenomas by ammonium perfluorooctanoate: a possible endocrine-related mechanism	1992	Toxicol Appl Pharmacol. 1992 Apr;113(2):209-17. doi: 10.1016/0041-008x(92)90116-a.	Ammonium perfluorooctanoate (C8) produced an increased incidence of Leydig cell adenomas in Crl:CD BR (CD) rats fed 300 ppm for 2 years. A hormonal (nongenotoxic) mechanism was examined since C8 was negative in short-term tests for genotoxicity. Adult male CD rats were gavaged with either 0, 1, 10, 25, or 50 mg/kg C8 for 14 days. In addition, a control group was pair-fed to the 50 mg/kg C8 group. A dose-dependent decrease in body and relative accessory sex organ (ASO) weights was seen, with the relative ASO weights of the 50 mg/kg group significantly less than those of the pair-fed control. Serum estradiol levels were elevated in the 10, 25, and 50 mg/kg C8-treated animals. Estradiol levels in the 50 mg/kg C8 group were 2.7-fold greater than those in the pair-fed control. The increase in serum estradiol levels occurred at the same dose levels as the increase in hepatic beta-oxidation activity. A statistically significant downward trend with dose was seen in serum testosterone levels when compared with the ad libitum control. However, when the 50 mg/kg C8-treated rats were compared with their pair-fed control, no significant differences were seen. Challenge experiments, which can identify the presence and location of a lesion in an endocrine axis, were undertaken to clarify the significance of this downward trend in serum testosterone following C8 exposure. In the challenge experiments, adult CD rats were gavaged with either 0 or 50 mg/kg C8 for 14 days. One hour before termination, rats received either a human chorionic gonadotropin (hCG), gonadotropin-releasing hormone (GnRH), or naloxone challenge. Following hCG challenge, serum testosterone levels in the 50 mg/kg C8 were significantly decreased -0.5 from those in the ad libitum controls. Similar decreases, although not significant, were seen in serum testosterone following GnRH and naloxone challenge. The challenge experiments suggest that the decrease in serum testosterone following C8 exposure is due to a lesion at the level of the testis. In addition, progesterone, 17 alpha-hydroxyprogesterone, and androstenedione were examined in the 50 mg/kg C8-treated males following hCG challenge. A 0.6 decrease was observed in androstenedione levels in the C8-treated animals from those in the ad libitum controls; no other differences were seen. These data suggest that the decrease in serum testosterone following hCG challenge may be due to a decrease in the conversion of 17 alpha-hydroxyprogesterone to androstenedione. The observed effects described above can be attributed to the elevated serum estradiol	●	●		●						-		1	B	A
1518	MOA（内分泌系）	Huhtaniemi, I; Toppari, J.	Endocrine, paracrine and autocrine regulation of testicular steroidogenesis	1995	Adv Exp Med Biol. 1995;377:33-54. doi: 10.1007/978-1-4899-0952-7_3.	Testicular steroidogenesis takes place almost exclusively in Leydig cells. Some metabolism of the androgens produced by Leydig cells takes place in seminiferous tubules, especially in the immature animal (e.g. aromatization and 5α-reduction). Luteinizing hormone (LH) is the main tropic regulator of Leydig cell function, without which quantitatively important androgen production is not possible. LH acts through a receptor that belongs to the seven times cell membrane spanning, G protein associated, receptor family, and cyclic AMP is the main second messenger of its signal transduction. Information about the involvement of other signal transduction systems in LH action has also emerged recently. The action of LH is under manyfold modulation by other hormones (e.g. prolactin, growth hormone and insulin), growth factors and bioactive peptides. In this modulation, various paracrine and autocrine mechanisms play an important role. Seminiferous tubules influence the development and function of adjacent Leydig cells through several growth factors. When germ cells are damaged, Leydig cells in the vicinity proliferate faster. Leydig cell morphology also depends on the germ cell composition in the neighbouring seminiferous tubules, and certain stages of the seminiferous epithelial cycle increase the Leydig cell capacity to produce testosterone. Also negative modulation of Leydig cells by Sertoli/germinal cell derived factors has been demonstrated. However, the physiological importance of the paracrine and modulatory influences of the different hormones and growth factors still remains obscure since almost all information has so far been obtained from in vitro studies. In the study of testicular steroidogenesis, the main switch of the function, LH action, is well known whereas the role of the “in house” circuits of paracrine and autocrine regulation remain to be elucidated.	●	●								-			D	C
1519	実験動物（内分泌系）	Martin, Matthew T; Brennan, Richard J; Hu, Wenyue; Ayanoglu, Eser; Lau, Christopher; Ren, Hongzu; Wood, Carmen R; Corton, J Christopher; Kavlock, Robert J; Dix, David J	Toxicogenomic study of triazole fungicides and perfluoroalkyl acids in rat livers predicts toxicity and categorizes chemicals based on mechanisms of toxicity	2007	Toxicol Sci. 2007 Jun;97(2):595-613. doi: 10.1093/toxsci/kfm065. Epub 2007 Mar 22.	Toxicogenomic analysis of five environmental chemicals was performed to investigate the ability of genomics to predict toxicity, categorize chemicals, and elucidate mechanisms of toxicity. Three triazole antifungals (myclobutanil, propiconazole, and triadimefon) and two perfluorinated chemicals [perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS)] were administered daily via oral gavage for one, three, or five consecutive days to male Sprague-Dawley rats at single doses of 300, 300, 175, 20, or 10 mg/kg/day, respectively. Clinical chemistry, hematology, and histopathology were measured at all time points. Gene expression profiling of livers from three rats per treatment group at all time points was performed on the CodeLink Uniset Rat I Expression array. Data were analyzed in the context of a large reference toxicogenomic database containing gene expression profiles for over 630 chemicals. Genomic signatures predicting hepatomegaly and hepatic injury preceded those results for all five chemicals, and further analysis segregated chemicals into two distinct classes. The triazoles caused similar gene expression changes as other azole antifungals, particularly the induction of pregnane X receptor (PXR)-regulated xenobiotic metabolism and oxidative stress genes. In contrast, PFOA and PFOS exhibited peroxisome proliferator-activated receptor alpha agonist-like effects on genes associated with fatty acid homeostasis. PFOA and PFOS also resulted in downregulation of cholesterol biosynthesis genes, matching an in vivo decrease in serum cholesterol, and perturbation of thyroid hormone metabolism genes matched by serum thyroid hormone depletion in vivo. The concordance of in vivo observations and gene expression findings demonstrated the ability of genomics to accurately categorize chemicals, identify toxic mechanisms of action, and predict subsequent pathological responses.	●	●		●	●	●				-			B	B
1520	実験動物（内分泌系）	Pereiro, N.; Moyano, R.; Blanco, A.; Lafuente, A.	Regulation of corticosterone secretion is modified by PFOS exposure at different levels of the hypothalamic-pituitary-adrenal axis in adult male rats	2014	Toxicol Lett. 2014 Oct 15;230(2):252-62. doi: 10.1016/j.toxlet.2014.01.003. Epub 2014 Jan 17.	Perfluorooctane sulfonate (PFOS) is a fluorinated compound and a Persistent Organic Pollutant which can disrupt the endocrine system. This work was undertaken to evaluate the possible effects of PFOS exposure on the regulation of corticosterone secretion in adrenal and pituitary glands and at hypothalamic level in adult male rat, and to evaluate the possible morphological alterations induced by PFOS in this endocrine tissue. Adult male rats were orally treated with 0.5, 1.0, 3 and 6.0mg of PFOS/kg/day for 28 days. Corticosterone, adrenocorticotropic hormone (ACTH) and corticotrophin-releasing hormone (CRH) secretion decreased in PFOS-treated rats. After PFOS exposure, relative expression of adrenocorticotropic hormone receptor (ACTHr) and proopiomelanocortin (POMC) genes was increased in adrenal and in pituitary glands, respectively; while relative expression of ACTHr and CRH genes decreased in hypothalamus with the doses of 0.5 and 1.0mg/kg/day. PFOS treatment increased relative nitric oxide synthase 1 and 2 (NOS1 and NOS2) gene expression in the adrenal gland, and incremented superoxide dismutase activity. PFOS exposure induces a global inhibition of the hypothalamic-pituitary-adrenal (HPA) axis activity, and small morphological changes were observed in adrenal zona fasciculata cells.	●	●		●						-		1	B	A
1521	実験動物（内分泌系）	Salgado, R.; Pereiro, N.; López-Doval, S.; Lafuente, A.	Initial study on the possible mechanisms involved in the effects of high doses of perfluorooctane sulfonate (PFOS) on prolactin secretion	2015	Food Chem Toxicol. 2015 Sep;83:10-6. doi: 10.1016/j.fct.2015.05.013. Epub 2015 May 30.	Perfluorooctane sulfonate (PFOS) is a fluorinated organic compound. This chemical is neurotoxic and can alter the pituitary secretion. This is an initial study aimed at knowing the toxic effects of high doses of PFOS on prolactin secretion and the possible mechanisms involved in these alterations. For that, adult male rats were orally treated with 3 and 6 mg of PFOS/kg body weight (b.w.)/day for 28 days. At the end of the treatment, the serum levels of prolactin and estradiol as well as the concentration of dopamine, 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA) and gamma-aminobutyric acid (GABA) were quantified in the anterior and in the mediobasal hypothalamus. PFOS, at the administered doses, reduced prolactin and estradiol secretion, increased the concentration of dopamine and GABA in the anterior hypothalamus, and decreased the ratios DOPAC/dopamine and HVA/dopamine in this same hypothalamic area. The outcomes reported in this study suggest that -1 high doses of PFOS inhibit prolactin secretion in adult male rats; -2 only the periventricular-hypophysial dopaminergic (PHDA) neurons seem to be involved in this inhibitory effect but not the tuberoinfundibular dopaminergic (TIDA) and the tuberohypophysial dopaminergic (THDA) systems; -3 GABAergic cells from the paraventricular and supraoptic nuclei could be partially responsible for the PFOS action on prolactin secretion; and finally -4 estradiol might take part in the inhibition exerted by elevated concentration of PFOS on prolactin release.	●	●		●						-		1	A	A

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	情報抽出	文献クラン①抽出	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022					
1522	実験動物（内分泌系）	Salgado-Freiría, R.; López-Doval, S.; Lafuente, A.	Perfluorooctane sulfonate (PFOS) can alter the hypothalamic-pituitary-adrenal (HPA) axis activity by modifying CRF1 and glucocorticoid receptors	2018	Toxicol Lett. 2018 Oct 1;295:1-9. doi: 10.1016/j.toxlet.2018.05.025. Epub 2018 May 26.	Perfluorooctane sulfonate (PFOS) is an endocrine disruptor highly persistent, bioaccumulative and neurotoxic, whose presence has been detected in different compartments of the environment. The aim of this study was to investigate whether PFOS could alter the HPA axis activity by modifying the gene and protein expression of corticotropin-releasing factor 1 receptor (CRF1r) and glucocorticoid receptor (Gr). For that purpose, Sprague-Dawley adult male rats were orally treated by gavage with 0.5; 1.0; 3 and 6.0 mg of PFOS/kg/day for 28 consecutive days. After PFOS administration, gene and protein expression of CRF1r were analysed in the hypothalamus, hippocampus, pituitary and adrenal glands. Moreover, Gr gene and protein expression were measured in hypothalamus, pituitary gland, prefrontal cortex, amygdala and hippocampus. The reported results indicate that -1 PFOS could inhibit HPA axis activity by diminishing gene and protein expression of CRF1r in the pituitary gland; -2 PFOS inhibits Gr protein expression in both prefrontal cortex and amygdala, which could be related to the toxic effects of this contaminant in this neuroendocrine axis and finally, -3 PFOS-treated rats would try to maintain the physiological levels of corticosterone by reducing the protein expression of Gr in the pituitary gland.	●	●								-		1	B	A
1523	実験動物（内分泌系）	Sun, S.; Wang, J.; Lu, Y.; Dai, J.	Corticosteroid-binding globulin, induced in testicular Leydig cells by perfluorooctanoic acid, promotes steroid hormone synthesis	2018	Arch Toxicol. 92: 2013-2025. doi: 10.1007/s00204-018-2207-y. Epub 2018 May 2.	Perfluorooctanoic acid (PFOA) is an abundant perfluoroalkyl substance widely applied in industrial and consumer products. It is a ubiquitous environmental pollutant and suspected endocrine disruptor. Corticosteroid-binding globulin (CBG) is a monomeric glycoprotein that can bind specifically to anti-inflammatory steroids, such as glucocorticoids and progesterone, in circulation. Our previous proteomic profile analysis revealed that CBG levels increased in testes after PFOA treatment. In the present study, we verified its increase in mouse testes following oral exposure to PFOA (0, 1.25 and 5 mg/kg/day for 28 days) by immunohistochemical analysis and Western blotting. In addition, RNA fluorescence in situ hybridization (FISH) confirmed that testicular CBG was specifically expressed in Leydig cells. Serum CBG levels in all three PFOA groups also increased, accompanied by increased corticosterone in the 5 and 20 mg/kg/day groups and decreased adrenocorticotropic hormone in the 20 mg/kg/day group. Thus, the influence of PFOA on blood CBG may change free steroid hormone concentrations, thereby serving as an endocrine disruptor. A stimulation effect of PFOA on CBG was also observed in vitro using the Leydig tumor mLTC-1 cell line. Overexpression of CBG in mLTC-1 cells increased progesterone release in culture media. In addition, CBG-induced proteins involved in steroidogenesis in mLTC-1 cells, including steroidogenic acute regulatory protein (StAR), cytochrome P450 cholesterol side-chain cleavage enzyme (CYP11A1), 17α-hydroxylase/17,20 lyase (CYP17A1), and 3β-hydroxysteroid dehydrogenase (3β-HSD), which may be the mechanism behind increased progesterone. Furthermore, the production and release of CBG in mLTC-1 cells were also induced by luteinizing hormone, though this mechanism requires further exploration.	●	●								-			B	B
1524	MOA（内分泌系）	Weiss, Jana M; Andersson, Patrik L; Lamoree, Marja H; Leonards, Pim E G; van Leeuwen, Stefan P J; Hamers, Timo	Competitive Binding of Poly- and Perfluorinated Compounds to the Thyroid Hormone Transport Protein Transthyretin	2009	Toxicol Sci. 2009 Jun;109(2):206-16. doi: 10.1093/toxsci/kfp055. Epub 2009 Mar 17.	Due to their unique surfactant properties, poly- and perfluorinated compounds (PFCs) have been extensively used and can be found all over the environment. Concern about their environmental fate and toxicological properties has initiated several research projects. In the present study, we investigated if PFCs can compete with thyroxine (T(4), i.e., the transport form of thyroid hormone) for binding to the human thyroid hormone transport protein transthyretin (TTR). Such competitive capacity may lead to decreased thyroid hormone levels as previously reported for animals exposed to PFCs. Twenty-four PFCs, together with 6 structurally similar natural fatty acids, were tested for binding capacity in a radioligand-binding assay. The binding potency decreased in the order: perfluorohexane sulfonate > perfluorooctane sulfonate/perfluorooctanoic acid > perfluoroheptanoic acid > sodium perfluoro-1-octanesulfinate > perfluorononanoic acid, with TTR binding potencies 12.5-50 times lower than the natural ligand T(4). Some lower molecular weight compounds with structural similarity to these PFCs were > 100 times less potent than T(4). Simple descriptors based on the two-dimensional molecular structures of the compounds were used to visualize the chemical variation and to model the structure-activity relationship for the competitive potencies of the TTR-binding compounds. The models indicated the dependence on molecular size an binding of PFCs to TTR, as observed for human TTR in the present study, may explain altered thyroid hormone levels described for PFC-exposed rats and monkeys. Median human blood levels of the most potent TTR-binding PFCs are one to two orders of magnitude lower than concentration at 50% inhibition (IC(50)) values determined in the present study. In addition, this study contributes to the understanding of the bioaccumulation of PFCs in man and possibly in other wildlife species.d functional groups but demanded a more detailed description of the chemical properties and data for validation and further quantitative structure-activity relationship (QSAR) development. Competitive	●	●	●				●		●	-			A	B
1525	実験動物（内分泌系）	Yao, P. L.; Ehresman, D. J.; Rae, J. M.; Chang, S. C.; Frame, S. R.; Butenhoff, J. L.; Kennedy, G. L.; Peters, J. M.	Comparative in vivo and in vitro analysis of possible estrogenic effects of perfluorooctanoic acid	2014	Toxicology. 326: 62-73. 2014 Dec 4;326:62-73. doi: 10.1016/j.tox.2014.10.008. Epub 2014 Oct 18.	Previous studies suggested that perfluorooctanoate (PFOA) could activate the estrogen receptor (ER). The present study examined the hypothesis that PFOA can activate ER using an in vivo uterotrophic assay in CD-1 mice and an in vitro reporter assay. Pre-pubertal female CD-1 mice fed an estrogen-free diet from postnatal day (PND)14 through weaning on PND18 were administered 0, 0.005, 0.01, 0.02, 0.05, 0.1, or 1mg/kg PFOA or 17β-estradiol (E2, 0.5mg/kg) from PND18-20. In contrast to E2, PFOA caused no changes in the relative uterine weight, the expression of ER target genes, or the morphology of the uterus/cervix and/or vagina on PND21. Treatment of a stable human cell line containing an ER-dependent luciferase reporter construct with a broad concentration range of PFOA caused no change in ER-dependent luciferase activity; whereas E2 caused a marked increase of ER-dependent luciferase activity. These data indicate that PFOA does not activate mouse or human ER.	●	●		●						-			B	B
1526	実験動物（生殖発生毒性）	Yu, W. G.; Liu, W.; Jin, Y. H.; Liu, X. H.; Wang, F. Q.; Liu, L.; Nakayama, S. F.	Prenatal and postnatal impact of perfluorooctane sulfonate (PFOS) on rat development: a cross-foster study on chemical burden and thyroid hormone system	2009	Environ Sci Technol. 2009 Nov 1;43(21):8416-22. doi: 10.1021/es901602d.	Perfluorooctane sulfonate (PFOS), an environmentally persistent organic pollutant, has been reported to be transferred to the developing organisms via both placenta and breast milk. A cross-foster model was used to determine whether prenatal or postnatal exposure to PFOS alone can disturb the TH homeostasis in rat pups, and if so, which kind of exposure is a major cause of TH level alteration. Pregnant rats were fed standard laboratory rodent diet containing 0 (control) or 3.2 mg PFOS/kg throughout gestation and lactation period. On the day of birth, litters born to treated and control dams were cross-fostered, resulting in the following groups: unexposed control (CC), pups exposed only prenatally (TC), only postnatally (CT) or both prenatally and postnatally (TT). Serum and liver PFOS concentrations, serum total thyroxine (T4), total triiodothyronine (T3), reverse T3 (rT3) levels, and hepatic expression of genes involved in TH transport, metabolism, and receptors were evaluated in pups at the age of postnatal days (PNDs) 0, 7, 14, 21, or 35 PFOS body burden level in pups in group CT increased, while those in group TC dropped as they aged. Neither total T3 nor rT3 in pups was affected by PFOS exposure. Gestational exposure to PFOS alone (TC) significantly (p < 0.05) decreased T4 level in pups on PNDs 21 and 35, 20.3 and 0.194 lower than the control on the same PND, respectively. Postnatal exposure to PFOS alone (CT) also induced T4 depression on PNDs 21 and 35, 28.6 and 0.359 lower than controls, respectively. No significant difference in T4 level (p > 0.05) was observed between TC and CT on these two time points. None of the selected TH related transcripts was affected by PFOS in pups on PND 0 Only transcript level of transthyretin, TH binding protein, in group TT significantly increased to 1.5 of the control on PND 21 The results showed that prenatal PFOS exposure and postnatal PFOS exposure induced hypothyroxinemia in rat pups to a similar extent, which suggested that in utero PFOS exposure and postnatal PFOS accumulation, especially though maternal milk, are matters of great concern.	●	●		●						-		1	B	A
1527	in vitro（内分泌系）	Chang, Shu-Ching; Thibodeaux, Julie R; Eastvold, Mary L; Ehresman, David J; Bjork, James A; Froehlich, John W; Lau, Christopher S; Singh, Ravinder J; Wallace, Kendall B; Butenhoff, John L	Negative bias from analog methods used in the analysis of free thyroxine in rat serum containing perfluorooctanesulfonate (PFOS)	2007	Toxicology. 2007 May 5;234(1-2):21-33. doi: 10.1016/j.tox.2007.01.020. Epub 2007 Feb 4.	Decreases in serum total thyroxine (TT4) and free thyroxine (FT4) without a compensatory rise in thyroid stimulating hormone (thyrotropin or TSH) or histological changes of the thyroid have been observed in studies with perfluorooctanesulfonate (PFOS) treatments in rats. Prior observations do not fit the clinical profile of a hypothyroid state. PFOS is known to compete with fatty acids for albumin binding, and serum free fatty acids (FFA) are known to interfere with FT4 measurement using analog methods due to competition for protein binding. Therefore, we hypothesized that measured decreases in serum FT4 by analog methods in the presence of PFOS were due to carrier protein binding interference. We compared FT4 analog assay methods with a reference method using equilibrium dialysis (ED-RIA) for FT4 measurement in rat sera in vitro and in vivo. We also measured hepatic malic enzyme mRNA transcripts and activity as a marker for hepatic thyroid hormone response. PFOS did not reduce serum TT4 and FT4 in vitro at concentrations up to 200 microM. After three daily 5mg/kg oral doses of potassium PFOS to female rats, serum TSH and FT4 by ED-RIA were unchanged (although FT4 determined by two common analog methods was decreased), and malic enzyme was not suppressed. These data suggest that prior reports of reduced free thyroid hormone in the presence of PFOS were due to negative bias in analog methods and that short-term PFOS treatment does not suppress the physiological thyroid status in rats. A reference method such as ED-RIA should be used for determination of serum FT4 in the presence of PFOS.			●							-			C	B
1528	MOA（乳腺）	Gimble, J M; Pighetti, G M; Lerner, M R; Wu, X; Lightfoot, S A; Brackett, D J; Darcy, K; Hollingsworth, A B	Expression of peroxisome proliferator activated receptor mRNA in normal and tumorigenic rodent mammary glands	1998	Biochem Biophys Res Commun. 1998 Dec 30;253(3):813-7. doi: 10.1006/bbrc.1998.9858.	The peroxisome proliferator activated receptors (PPARs) alpha, beta/delta, and gamma are novel nuclear hormone receptors activated by long chain fatty acids and synthetic ligands and which regulate lipid metabolism. Recent studies have detected PPARgamma mRNA in human mammary tumor cell lines. The current study examined the expression profile of PPAR mRNAs in normal and malignant rodent mammary tissues. Virgin murine mammary glands contained PPAR alpha, beta/delta, and gamma mRNAs based on northern blot analysis. The PPARgamma isoform was predominantly gamma2 based on quantitative PCR analysis. During pregnancy and lactation, the PPARalpha and gamma mRNAs decreased while the PPAR beta/delta mRNA remained relatively unchanged. NMuMG cells, an epithelial line derived from normal murine mammary gland, expressed PPAR alpha, beta/delta, and gamma mRNAs, independent of the presence or absence of compounds modifying PPAR activity. In rats, the physiologic expression pattern of PPARgamma mRNA paralleled the murine model; levels were detected in virgin but not lactating mammary glands. In addition, the PPARgamma mRNA was not detected in several histologically distinct 7,12-dimethylbenz(a)anthracene induced mammary tumors. These findings suggest that PPARs may regulate mammary epithelial and stromal cell function in response to physiologic or pathologic stimuli that profoundly alter lipid metabolism.			●							-			C	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献ランク①	文献ランク②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1529	MOA（乳腺）	Halsne, Ruth; Tandberg, Julia Isabel; Lobert, Viola Hélène; Østby, Gunn Charlotte; Thoen, Even; Ropstad, Erik; Verhaegen, Steven	Effects of perfluorinated alkyl acids on cellular responses of MCF-10A mammary epithelial cells in monolayers and on acini formation in vitro	2016	Toxicol Lett. 2016 Sep 30;259:95-107. doi: 10.1016/j.toxlet.2016.08.004. Epub 2016 Aug 7.	Perfluorinated alkyl acids (PFAAs) are stable chemicals detected in tissue and serum from various species, including humans, and have been linked to adverse health outcomes. Experimental PFAA exposure in rodents has been associated with changes in mammary gland development. The estrogen receptor (ER)-negative human breast epithelial cell line, MCF-10A, can be grown as monolayer, but also has the ability to form three-dimensional acini in vitro, reflecting aspects of mammary glandular morphogenesis. Cells were exposed to five different PFAAs, perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), and perfluoroundecanoic acid (PFUnDA), both in monolayer and acini cultures. In monolayer cultures only the higher concentrations of PFOS, PFNA and PFDA (400-500μM) caused a significant increase in cell death, whereas PFOA and PFUnDA had no effect. Normal acini maturation was negatively impacted by PFOS, PFNA and PFDA already at the lowest concentration tested (0.6μM). Observed effects included loss of organization of the cell clusters and absence of a hollow lumen. Overall, this study demonstrated that PFAAs can interfere with cellular events related to normal development of glandular breast tissue through ER-independent mechanisms.			●							-		B	B
1530	MOA（乳腺）	Macias, Hector; Hinck, Lindsay	Mammary gland development	2012	Wiley Interdiscip Rev Dev Biol. 2012 Jul-Aug;1(4):533-57. doi: 10.1002/wdev.35.	The mammary gland develops through several distinct stages. The first transpires in the embryo as the ectoderm forms a mammary line that resolves into placodes. Regulated by epithelial–mesenchymal interactions, the placodes descend into the underlying mesenchyme and produce the rudimentary ductal structure of the gland present at birth. Subsequent stages of development—pubertal growth, pregnancy, lactation, and involution—occur postnatally under the regulation of hormones. Puberty initiates branching morphogenesis, which requires growth hormone (GH) and estrogen, as well as insulin-like growth factor 1 (IGF1), to create a ductal tree that fills the fat pad. Upon pregnancy, the combined actions of progesterone and prolactin generate alveoli, which secrete milk during lactation. Lack of demand for milk at weaning initiates the process of involution whereby the gland is remodeled back to its prepregnancy state. These processes require numerous signaling pathways that have distinct regulatory functions at different stages of gland development. Signaling pathways also regulate a specialized subpopulation of mammary stem cells that fuel the dramatic changes in the gland occurring with each pregnancy. Our knowledge of mammary gland development and mammary stem cell biology has significantly contributed to our understanding of breast cancer and has advanced the discovery of therapies to treat this disease.			●							-		D	C
1531	MOA（乳腺）	Martinson, Holly A; Lyons, Traci R; Giles, Erin D; Borges, Virginia F; Schedin, Pepper	Developmental windows of breast cancer risk provide opportunities for targeted chemoprevention	2013	Exp Cell Res. 2013 Jul 1;319(11):1671-8. doi: 10.1016/j.yexcr.2013.04.018. Epub 2013 May 9.	The magnitude of the breast cancer problem implores researchers to aggressively investigate prevention strategies. However, several barriers currently reduce the feasibility of breast cancer prevention. These barriers include the inability to accurately predict future breast cancer diagnosis at the individual level, the need for improved understanding of when to implement interventions, uncertainty with respect to optimal duration of treatment, and negative side effects associated with currently approved chemoprevention therapies. None-the-less, the unique biology of the mammary gland, with its postnatal development and conditional terminal differentiation, may permit the resolution of many of these barriers. Specifically, lifecycle-specific windows of breast cancer risk have been identified that may be amenable to risk-reducing strategies. Here, we argue for prevention research focused on two of these lifecycle windows of risk: postpartum mammary gland involution and peri-menopause. We provide evidence that these windows are highly amenable to targeted, limited duration treatments. Such approaches could result in the prevention of postpartum and postmenopausal breast cancers, correspondingly.			●							-		D	C
1532	in vitro（発がん性）	Pierozan, Paula; Karlsson, Oskar	PFOS induces proliferation, cell-cycle progression, and malignant phenotype in human breast epithelial cells	2018	Arch Toxicol. 2018 Feb;92(2):705-716. doi: 10.1007/s00204-017-2077-8. Epub 2017 Oct 23.	Perfluorooctanesulfonic acid (PFOS) is a synthetic fluorosurfactant widely used in the industry and a prominent environmental toxicant. PFOS is persistent, bioaccumulative, and toxic to mammalian species. Growing evidence suggests that PFOS has the potential to interfere with estrogen homeostasis, posing a risk of endocrine-disrupting effects. Recently, concerns about a potential link between PFOS and breast cancer have been raised, but the mechanisms underlying its actions as a potential carcinogen are unknown. By utilizing cell proliferation assays, flow cytometry, immunocytochemistry, and cell migration/invasion assays, we examined the potentially tumorigenic activity of PFOS (100 nM-1 mM) in MCF-10A breast cell line. The results showed that the growth of MCF-10A cells exposed to 1 and 10 μM PFOS was higher compared to that of the control. Mechanistic studies using 10 μM PFOS demonstrated that the compound promotes MCF-10A proliferation through accelerating G(0)/G(1-)to-S phase transition of the cell cycle after 24, 48, and 72 h of treatment. In addition, PFOS exposure increased CDK4 and decreased p27, p21, and p53 levels in the cells. Importantly, treatment with 10 μM PFOS for 72 h also stimulated MCF-10A cell migration and invasion, illustrating its capability to induce neoplastic transformation of human breast epithelial cells. Our experimental results suggest that exposure to low levels of PFOS might be a potential risk factor in human breast cancer initiation and development.			●							-		B	A
1533	MOA（乳腺）	Qu, Ying; Han, Bingchen; Yu, Yi; Yao, Weiwu; Bose, Shikha; Karlan, Beth Y; Giuliano, Armando E; Cui, Xiaojiang	Evaluation of MCF10A as a reliable model for normal human mammary epithelial cells	2015	PLoS One. 2015 Jul 6;10(7):e0131285. doi: 10.1371/journal.pone.0131285. eCollection 2015.	Breast cancer is the most common cancer in women and a leading cause of cancer-related deaths for women worldwide. Various cell models have been developed to study breast cancer tumorigenesis, metastasis, and drug sensitivity. The MCF10A human mammary epithelial cell line is a widely used in vitro model for studying normal breast cell function and transformation. However, there is limited knowledge about whether MCF10A cells reliably represent normal human mammary cells. MCF10A cells were grown in monolayer, suspension (mammosphere culture), three-dimensional (3D) "on-top" Matrigel, 3D "cell-embedded" Matrigel, or mixed Matrigel/collagen I gel. Suspension culture was performed with the MammoCult medium and low-attachment culture plates. Cells grown in 3D culture were fixed and subjected to either immunofluorescence staining or embedding and sectioning followed by immunohistochemistry and immunofluorescence staining. Cells or slides were stained for protein markers commonly used to identify mammary progenitor and epithelial cells. MCF10A cells expressed markers representing luminal, basal, and progenitor phenotypes in two-dimensional (2D) culture. When grown in suspension culture, MCF10A cells showed low mammosphere-forming ability. Cells in mammospheres and 3D culture expressed both luminal and basal markers. Surprisingly, the acinar structure formed by MCF10A cells in 3D culture was positive for both basal markers and the milk proteins β-casein and α-lactalbumin. MCF10A cells exhibit a unique differentiated phenotype in 3D culture which may not exist or be rare in normal human breast tissue. Our results raise a question as to whether the commonly used MCF10A cell line is a suitable model for human mammary cell studies.			●							-		D	C
1534	MOA（甲状腺）	Ren, Xiao-Min; Zhang, Yin-Feng; Guo, Liang-Hong; Qin, Zhan-Fen; Lv, Qi-Yan; Zhang, Lian-Ying	Structure-activity relations in binding of perfluoroalkyl compounds to human thyroid hormone T3 receptor	2015	Arch Toxicol. 2015 Feb;89(2):233-42. doi: 10.1007/s00204-014-1258-y. Epub 2014 May 13.	Perfluoroalkyl compounds (PFCs) have been shown to disrupt thyroid functions through thyroid hormone receptor (TR)-mediated pathways, but direct binding of PFCs with TR has not been demonstrated. We investigated the binding interactions of 16 structurally diverse PFCs with human TR, their activities on TR in cells, and the activity of perfluorooctane sulfonate (PFOS) in vivo. In fluorescence competitive binding assays, most of the 16 PFCs were found to bind to TR with relative binding potency in the range of 0.0003-0.05 compared with triiodothyronine (T3). A structure-binding relationship for PFCs was observed, where fluorinated alkyl chain length longer than ten, and an acid end group were optimal for TR binding. In thyroid hormone (TH)-responsive cell proliferation assays, PFOS, perfluorohexadecanoic acid, and perfluorooctadecanoic acid exhibited agonistic activity by promoting cell growth. Furthermore, similar to T3, PFOS exposure promoted expression of three TH upregulated genes and inhibited three TH downregulated genes in amphibians. Molecular docking analysis revealed that most of the tested PFCs efficiently fit into the T3-binding pocket in TR and formed a hydrogen bond with arginine 228 in a manner similar to T3. The combined in vitro, in vivo, and computational data strongly suggest that some PFCs disrupt the normal activity of TR pathways by directly binding to TR.			●							-		B	D
1535	MOA（内分泌系）	Ren, Xiao-Min; Qin, Wei-Ping; Cao, Lin-Ying; Zhang, Jing; Yang, Yu; Wan, Bin; Guo, Liang-Hong	Binding interactions of perfluoroalkyl substances with thyroid hormone transport proteins and potential toxicological implications	2016	Toxicology. 2016 Jul 29;366-367:32-42. doi: 10.1016/j.tox.2016.08.011. Epub 2016 Aug 12.	Perfluoroalkyl substances (PFASs) have been shown to cause abnormal levels of thyroid hormones (THs) in experimental animals, but the molecular mechanism is poorly understood. Here, a fluorescence displacement assay was used to determine the binding affinities of 16 PFASs with two major TH transport proteins, transthyretin (TTR) and thyroxine-binding globulin (TBG). Most of the tested PFASs bound TTR with relative potency (RP) values of 3×10(-4) to 0.24 when compared with that of the natural ligand thyroxine, whereas fluorotelomer alcohols did not bind. Only perfluorotridecanoic acid and perfluorotetradecanoic acid bound TBG, with RP values of 2 ×10(-4) when compared with that of thyroxine. Based on these results, it was estimated that displacement of T4 from TTR by perfluorooctane sulfonate and perfluorooctanoic acids would be significant for the occupationally exposed workers but not the general population. Structure-binding analysis revealed that PFASs with a medium chain length and a sulfonate acid group are optimal for TTR binding, and PFASs with lengths longer than 12 carbons are optimal for TBG binding. Three mutant proteins were prepared to examine crucial residues involved in the binding of PFASs to TH transport proteins. TTR with a K15G mutation and TBG with either a R378G or R381G mutation showed decreased binding affinity to PFASs, indicating that these residues play key roles in the interaction with the compounds. Molecular docking showed that the PFASs bind to TTR with their acid group forming a hydrogen bond with K15 and the hydrophobic chain towards the interior. PFASs were modeled to bind TBG with their acid group forming a hydrogen bond with R381 and the hydrophobic chain extending towards R378. The findings aid our understanding of the behavior and toxicity of PFASs on the thyroid hormone system.			●				●			-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1536	MOA（内分泌系）	Rosenmai, A K; Taxvig, C; Svingen, T; Trier, X; van Vugt-Lussenburg, B M A; Pedersen, M; Lesné, L; Jégou, B; Vinggaard, A M	Fluorinated alkyl substances and technical mixtures used in food paper-packaging exhibit endocrine related activity in vitro	2016	Andrology. 2016 Jul;4(4):662-72. doi: 10.1111/andr.12190. Epub 2016 May 6.	Migration of chemicals from packaging materials to foods may lead to human exposure. Polyfluoroalkyl substances (PFAS) can be used in technical mixtures (TMs) for use in food packaging of paper and board, and PFAS have been detected in human serum and umbilical cord blood. The specific structures of the PFAS in TMs are often unknown, but polyfluorinated alkyl phosphate esters (PAPs) have been characterized in TMs, food packaging, and in food. PAPs can be metabolized into fluorotelomer alcohols (FTOHs) and perfluoroalkyl carboxylic acids (PFCAs). Some PFAS have endocrine activities, highlighting the need to investigate these effects. Herein, we studied the endocrine activity of less characterized PFAS, including short-chain PFCAs and FTOHs, PAPs, and TMs of unknown chemical composition. Long-chain PFCAs were also included. We applied seven assays covering effects on estrogen, glucocorticoid, androgen, and peroxisome proliferator-activated receptor (PPAR) activity, as well as steroidogenesis in vitro and ex vivo. In general, PAPs, FTOHs, TMs, and long-chain PFCAs showed estrogenic activity through receptor activation and/or increasing 17β-estradiol levels. Furthermore, short- and long-chain PFCAs activated PPARα and PPARγ. Collectively, this means that (i) PAPs, FTOHs, and PFCAs exhibit endocrine activity through distinct and sometimes different mechanisms, (ii) two out of three tested TMs exhibited estrogenic activity, and (iii) short-chain FTOHs showed estrogenic activity and short-chain PFCAs generally activate both PPARα and PPARγ with similar potency and efficacy as long-chain PFCAs. In conclusion, several new and divergent toxicological targets were identified for different groups of PFAS.			●							-		B	D
1537	MOA（内分泌系）	Rosenmai, Anna Kjerstine; Ahrens, Lutz; le Godec, Théo; Lundqvist, Johan; Oskarsson, Agneta	Relationship between peroxisome proliferator-activated receptor alpha activity and cellular concentration of 14 perfluoroalkyl substances in HepG2 cells	2018	J Appl Toxicol. 2018 Feb;38(2):219-226. doi: 10.1002/jat.3515. Epub 2017 Aug 31.	Peroxisome proliferator-activated receptor alpha (PPARα) is a molecular target for perfluoroalkyl substances (PFASs). Little is known about the cellular uptake of PFASs and how it affects the PPARα activity. We investigated the relationship between PPARα activity and cellular concentration in HepG2 cells of 14 PFASs, including perfluoroalkyl carboxylates (PFCAs), perfluoroalkyl sulfonates and perfluorooctane sulfonamide (FOSA). Cellular concentrations were determined by high-performance liquid chromatography-tandem mass spectrometry and PPARα activity was determined in transiently transfected cells by reporter gene assay. Cellular uptake of the PFASs was low (0.04-4.1%) with absolute cellular concentrations in the range 4-2500 ng mg(-1) protein. Cellular concentration of PFCAs increased with perfluorocarbon chain length up to perfluorododecanoate. PPARα activity of PFCAs increased with chain length up to perfluorooctanoate. The maximum induction of PPARα activity was similar for short-chain (perfluorobutanoate and perfluoropentanoate) and long-chain PFCAs (perfluorododecanoate and perfluorotetradecanoate) (approximately twofold). However, PPARα activities were induced at lower cellular concentrations for the short-chain homologs compared to the long-chain homologs. Perfluorohexanoate, perfluoroheptanoate, perfluorooctanoate, perfluorononanoate (PFNA) and perfluorodecanoate induced PPARα activities >2.5-fold compared to controls. The concentration-response relationships were positive for all the tested compounds, except perfluorooctane sulfonate PFOS and FOSA, and were compound-specific, as demonstrated by differences in the estimated slopes. The relationships were steeper for PFCAs with chain lengths up to and including PFNA than for the other studied PFASs. To our knowledge, this is the first report establishing relationships between PPARα activity and cellular concentration of a broad range of PFASs.			●							-		B	D
1538	MOA（乳腺）	Russo, J; Russo, I H	Experimentally induced mammary tumors in rats	1996	Breast Cancer Res Treat. 1996;39(1):7-20. doi: 10.1007/BF01806074.	Among the multiple experimental animal models employed for analyzing the various aspects of mammary carcinogenesis, the induction of mammary tumors in rats by chemical carcinogens is one of the models most utilized. Experimentally-induced mammary tumors in rodents have proven to constitute useful tools for the study of the pathogenesis of cancer and of the molecular mechanisms involved in the initiation and progression of the neoplastic process. In vivo experimental animal models provide information not available in human populations; they are adequate for hazard identification, dose-response modeling, exposure assessment, and risk characterization, the four required steps for quantifying the estimated risk of cancer development associated with toxic chemical exposure. Using the DMBA rat mammary model, we have been able to demonstrate that the carcinogen acts on the intermediate cell of the terminal end bud (TEB), and that this structure is the one that evolves to intraductal proliferation, carcinoma in situ, and invasive carcinoma. There are several factors that regulate the susceptibility of the TEB; some of them are: a) topographic location of the mammary gland, b) age of the animal, and c) reproductive history. The understanding of the mechanisms that modulate tumorigenesis will further our knowledge and understanding in the prevention of the disease, as a result of the development of strategies for stopping the progression of the initiated cells.			●							-		D	C
1539	MOA（乳腺）	Yang, Qian; Yamada, Atsushi; Kimura, Shioko; Peters, Jeffrey M; Gonzalez, Frank J	Alterations in Skin and Stratified Epithelia by Constitutively Activated PPARa	2006	J Invest Dermatol. 2006 Feb;126(2):374-85. doi: 10.1038/sj.jid.5700056.	Peroxisome proliferator-activated receptor (PPAR)alpha is a pleiotropic regulator in many cell types and has recently been implicated in skin homeostasis. To determine the role of PPARalpha in skin physiology, transgenic mice were generated using the tetracycline Tet-off regulatory system to target constitutively activated PPARalpha to the epidermis and other stratified epithelia by the bovine keratin K5 promoter. Expression of the transgene during early development resulted in postnatal lethality within 2 days after birth. A thin epidermis, few hair follicles, and abnormal development of the tongue were observed in neonatal transgenic mice. Early mortality was not observed when transgenic PPARalpha expression was diminished by administration of doxycycline (dox) to the mothers. The alterations noted in neonatal mice were not observed in adult mice upon re-expression of the PPARalpha transgene by withdrawing dox. Attenuated hyperplasia of interfollicular epidermis after topical application of the tumor promotor 12-O-tetradecanoyl-phorbol-13-acetate (TPA) was observed in adult mice expressing the PPARalpha transgene. In addition, expression of the PPARalpha transgene in mammary gland during pregnancy resulted in abnormal development of this organ and impaired lactation. Further investigations using primary keratinocytes revealed that expression of the transgene in keratinocytes resulted in increased differentiation and decreased proliferation, which may contribute to the observed phenotype in the transgenic mice. Thus, these results indicate that PPARalpha plays an important role in the development of stratified epithelia including skin, tongue, and mammary gland.			●							-		C	C
1540	MOA（乳腺）	Yang, Qian; Kurotani, Reiko; Yamada, Atsushi; Kimura, Shioko; Gonzalez, Frank J	PPARa activation during pregnancy severely impairs mammary lobuloalveolar development in mice	2006	Endocrinology. 2006 Oct;147(10):4772-80. doi: 10.1210/en.2006-0437. Epub 2006 Jul 20.	To identify the potential functions of peroxisome proliferator-activated receptor alpha (PPARalpha) in skin development, transgenic mice were generated to target constitutively activated PPARalpha (VP16PPARalpha) to the stratified epithelia by use of the keratin K5 promoter. In addition to marked alterations in epidermal development, the transgenic mice had a severe defect in lactation during pregnancy resulting in 100% pup mortality. In this study, the alteration of mammary gland development in these transgenic mice was investigated. The results showed that expression of the VP16PPARalpha transgene during pregnancy resulted in impaired development of lobuloalveoli, which is associated with reduced proliferation and increased apoptosis of mammary epithelia. Mammary epithelia from transgenic mice also showed a significant reduction in the expression of beta-catenin and a down-regulation of one of its target genes, cyclin D1, which is thought to be required for lobuloalveolar development. Furthermore, upon PPARalpha ligand treatment, similar effects on lobuloalveolar development were observed in wild-type mice, but not in PPARalpha-null mice. These findings suggest that PPARalpha activation has a marked influence in mammary lobuloalveolar development.			●							-		C	C
1541	MOA（乳腺）	Zhao, Yong; Tan, Ying S; Haslam, Sandra Z; Yang, Chengfeng	Perfluorooctanoic acid effects on steroid hormone and growth factor levels mediate stimulation of peripubertal mammary gland development in C57BL/6 mice	2010	Toxicol Sci. 2010 May;115(1):214-24. doi: 10.1093/toxsci/kfq030. Epub 2010 Jan 29.	Perfluorooctanoic acid (PFOA) is a synthetic, widely used perfluorinated carboxylic acid and a persistent environmental pollutant. It is an agonist of peroxisome proliferator-activated receptor alpha (PPARalpha). Studies have shown that PFOA causes hepatocellular hypertrophy, tumorigenesis, and developmental toxicity in rodents, and some of its toxicity depends on the expression of PPARalpha. Our recent study revealed a stimulatory effect of peripubertal PFOA treatment (5 mg/kg) on mammary gland development in C57Bl/6 mice. The present study was designed to examine the underlying mechanism(s). It was found that mammary gland stimulation by PFOA was similarly observed in PPARalpha knockout and wild-type C57Bl/6 mice. The presence of ovaries was required for PFOA treatment (5 mg/kg) to stimulate mammary gland development with significant increases in the levels of enzymes involved in steroid hormone synthesis in both PFOA-treated wild-type and PPARalpha knockout mouse ovaries. PFOA treatment significantly increased serum progesterone (P) levels in ovary-intact mice and also enhanced mouse mammary gland responses to exogenous estradiol (E), P, and E + P. In addition, PFOA treatment resulted in elevated mammary gland levels of epidermal growth factor receptor (EGFR), estrogen receptor alpha, amphiregulin (Areg, a ligand of EGFR), hepatocyte growth factor, cyclin D1, and proliferating cell nuclear antigen (PCNA) in both wild-type and PPARalpha knockout mouse mammary glands. These results indicate that PFOA stimulates mammary gland development in C57Bl/6 mice by promoting steroid hormone production in ovaries and increasing the levels of a number of growth factors in mammary glands, which is independent of the expression of PPARalpha.			●	●		●				-		B	B
1542	実験動物（内分泌系）	Benninghoff, Abby D; Bisson, William H; Koch, Daniel C; Ehresman, David J; Kolluri, Siva K; Williams, David E	Estrogen-like activity of perfluoroalkyl acids in vivo and interaction with human and rainbow trout estrogen receptors in vitro	2011	Toxicol Sci. 2011 Mar;120(1):42-58. doi: 10.1093/toxsci/kfq379. Epub 2010 Dec 16.	The objectives of this study were to determine the structural characteristics of perfluoroalkyl acids (PFAAs) that confer estrogen-like activity in vivo using juvenile rainbow trout (Oncorhynchus mykiss) as an animal model and to determine whether these chemicals interact directly with the estrogen receptor (ER) using in vitro and in silico species comparison approaches. Perfluorooctanoic (PFOA), perfluorononanoic (PFNA), perfluorodecanoic (PFDA), and perfluoroundecanoic (PFUnDA) acids were all potent inducers of the estrogen-responsive biomarker protein vitellogenin (Vtg) in vivo, although at fairly high dietary exposures. A structure-activity relationship for PFAAs was observed, where eight to ten fluorinated carbons and a carboxylic acid end group were optimal for maximal Vtg induction. These in vivo findings were corroborated by in vitro mechanistic assays for trout and human ER. All PFAAs tested weakly bound to trout liver ER with half maximal inhibitory concentration (IC(50)) values of 15.2-289 μM. Additionally, PFOA, PFNA, PFDA, PFUnDA, and perfluorooctane sulfonate (PFOS) significantly enhanced human ERα-dependent transcriptional activation at concentrations ranging from 10-1000 nM. Finally, we employed an in silico computational model based upon the crystal structure for the human ERα ligand-binding domain complexed with E2 to structurally investigate binding of these putative ligands to human, mouse, and trout ERα. PFOA, PFNA, PFDA, and PFOS all efficiently docked with ERα from different species and formed a hydrogen bond at residue Arg394/398/407 (human/mouse/trout) in a manner similar to the environmental estrogens bisphenol A and nonylphenol. Overall, these data support the contention that several PFAAs are weak environmental xenoestrogens of potential concern.			●							-	1	B	A

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報抽出対象	文献ランク①	文献ランク②
1543	実験動物（内分泌系）	Issemann I, Green S.	Activation of a member of a steroid hormone receptor superfamily by peroxisome proliferators	1990	Nature. 1990 Oct 18;347(6294):645-50. doi: 10.1038/347645a0.	We have cloned a member of the steroid hormone receptor superfamily of ligand-activated transcription factors. The receptor homologue is activated by a diverse class of rodent hepatocarcinogens that causes proliferation of peroxisomes. Identification of a peroxisome proliferator-activated receptor should help elucidate the mechanism of the hypolipidaemic effect of these hepatocarcinogens and aid evaluation of their potential carcinogenic risk to man.				●						-		D	C
1544	in vitro（内分泌系）	Kjeldsen, Lisbeth Stigaard; Bonefeld-Jørgensen, Eva Cecilie	Perfluorinated compounds affect the function of sex hormone receptors	2013	Environ Sci Pollut Res Int. 2013 Nov;20(11):8031-44. doi: 10.1007/s11356-013-1753-3. Epub 2013 Jun 14.	Perfluorinated compounds (PFCs) are a large group of chemicals used in different industrial and commercial applications. Studies have suggested the potential of some PFCs to disrupt endocrine homeostasis, increasing the risk of adverse health effects. This study aimed to elucidate mechanisms behind PFC interference with steroid hormone receptor functions. Seven PFCs [perfluorohexane sulfonate (PFHxS), perfluorooctane sulfonate (PFOS), perfluorooctanoate (PFOA), perfluorononanoate (PFNA), perfluorodecanoate (PFDA), perfluoroundecanoate (PFUnA), and perfluorododecanoate (PFDoA)] were analyzed in vitro for their potential to affect estrogen receptor (ER) and androgen receptor (AR) transactivity as well as aromatase enzyme activity. The PFCs were assessed as single compounds and in an equimolar mixture. PFHxS, PFOS and PFOA significantly induced the ER transactivity, whereas PFHxS, PFOS, PFOA, PFNA and PFDA significantly antagonized the AR activity in a concentration-dependent manner. Moreover, PFDA weakly decreased the aromatase activity at a high test concentration. A mixture effect more than additive was observed on AR function. We conclude that five of the seven PFCs possess the potential in vitro to interfere with the function of the ER and/or the AR. The observed mixture effect emphasizes the importance of considering the combined action of PFCs in future studies to assess related health risks.				●	●	●				-		B	B
1545	実験動物（生殖発生毒性）	Ribes, Diana; Fuentes, Silvia; Torrente, Margarita; Colomina, M Teresa; Domingo, José L	Combined effects of perfluorooctane sulfonate (PFOS) and maternal restraint stress on hypothalamus adrenal axis (HPA) function in the offspring of mice	2010	Toxicol Appl Pharmacol. 2010 Feb 15;243(1):13-8. doi: 10.1016/j.taap.2009.11.001. Epub 2009 Nov 10.	Although it is known that prenatal exposure to perfluorooctane sulfonate (PFOS) can cause developmental adverse effects in mammals, the disruptive effects of this compound on hormonal systems are still controversial. Information concerning the effects of PFOS on hypothalamus adrenal (HPA) axis response to stress and corticosterone levels is not currently available. On the other hand, it is well established that stress can enhance the developmental toxicity of some chemicals. In the present study, we assessed the combined effects of maternal restraint stress and PFOS on HPA axis function in the offspring of mice. Twenty plug-positive female mice were divided in two groups. Animals were given by gavage 0 and 6 mg PFOS/kg/day on gestation days 12-18. One half of the animals in each group were also subjected to restraint stress (30 min/session, 3 sessions/day) during the same period. Five plug-positive females were also included as non-manipulated controls. At 3 months of age, activity in an open-field and the stress response were evaluated in male and female mice by exposing them to 30 min of restraint stress. Male and female offspring were subsequently sacrificed and blood samples were collected to measure changes in corticosterone levels at four different moments related to stress exposure conditions: before stress exposure, immediately after 30 min of stress exposure, and recuperation levels at 60 and 90 min after stress exposure. Results indicate corticosterone levels were lower in mice prenatally exposed to restraint. In general terms, PFOS exposure decreased corticosterone levels, although this effect was only significant in females. The recuperation pattern of corticosterone was mainly affected by prenatal stress. Interactive effects between PFOS and maternal stress were sex dependent. The current results suggest that prenatal PFOS exposure induced long-lasting effects in mice.				●						-	1	B	A
1546	実験動物（内分泌系）	Wei, Yanhong; Dai, Jiayin; Liu, Min; Wang, Jianshe; Xu, Muqi; Zha, Jinmiao; Wang, Zijian	Estrogen-like properties of perfluorooctanoic acid as revealed by expressing hepatic estrogen-responsive genes in rare minnows (Gobiocyris rarus)	2007	Environ Toxicol Chem. 2007 Nov;26(11):2440-7. doi: 10.1897/07-008R1.1.	Perfluorooctanoic acid (PFOA) is an important perfluorinated compound (PFC) with various applications and has been widely disseminated in the environment, wildlife, and humans. The present study investigated the effects of waterborne PFOA on the expression of hepatic estrogen-responsive genes, vitellogenin (VTG), and estrogen receptor beta (ERbeta) and on the gonadal development in a freshwater rare minnow (Gobiocypris rarus). The mRNA levels of VTG and ERbeta were determined using reverse transcription polymerase chain reaction (RT-PCR) techniques, and VTG protein levels were identified using enzyme-linked immunosorbent assay. A significant increase of VTG expression in the livers of both mature males and females was observed after 14 and 28 d of exposure to 3, 10, and 30 mg/L PFOA, indicating that PFOA could induce VTG synthesis. The expression of ERbeta increased significantly in livers of both mature males and females after a 14-d exposure, although no difference was observed after a 28-d exposure. The development of oocytes in testes exposed to PFOA also provided evidence of estrogenic activity in males. The ovaries of PFOA-exposed females underwent degeneration, as reported in other fish species exposed to environmental estrogens. This preliminary study indicates that PFOA can disturb the activity of estrogen in mature male rare minnows by inducing hepatic estrogen-responsive genes, VTG and ERbeta, and barrier female reproduction.				●						-	1	B	A
1547	実験動物（内分泌系）	Austkin et al.	Neuroendocrine effects of perfluorooctane sulfonate in rats	2003	Environ Health Perspect. 111(12):1485-9. doi: 10.1289/ehp.6128.	Perfluorooctane sulfonate (PFOS) is a degradation product of sulfonyl-based fluorochemicals that are used extensively in industrial and household applications. Humans and wildlife are exposed to this class of compounds from several sources. Toxicity tests in rodents have raised concerns about potential developmental, reproductive, and systemic effects of PFOS. However, the effect of PFOS on the neuroendocrine system has not been investigated thus far. In this study, adult female rats were injected intraperitoneally with 0, 1, or 10 mg PFOS/kg body weight (BW) for 2 weeks. Food and water intake, BW, and estrous cycles were monitored daily. At the end of treatment, PFOS levels in tissues were measured by high-performance liquid chromatography (HPLC) interfaced with electrospray mass spectrometry. Changes in brain monoamines were measured by HPLC with electrochemical detection, and serum corticosterone and leptin were monitored using radioimmunoassay. Treatment with PFOS produced a dose-dependent accumulation of this chemical in various body tissues, including the brain. PFOS exposure decreased food intake and BW in a dose-dependent manner. Treatment with PFOS affected estrous cyclicity and increased serum corticosterone levels while decreasing serum leptin concentrations. PFOS treatment also increased norepinephrine concentrations in the paraventricular nucleus of the hypothalamus. These results indicate that exposure to PFOS can affect the neuroendocrine system in rats.					●					-		B	B
1548	実験動物（内分泌系）	Health Canada	Seacat reanalysis—statistical analysis of cynomolgus monkey data	2013	Internal report. Health Canada, Ottawa, Ontario.	No abstract available					●					Health Canada 評価資料？		D	D
1549	MOA（内分泌系）	Sonthithai, Pacharapan; Suriyo, Tawit; Thiantanawat, Apinya; Watcharasit, Piyajit; Ruchirawat, Mathuros; Satayavivad, Jutamaad	Perfluorinated chemicals, PFOS and PFOA, enhance the estrogenic effects of 17β-estradiol in T47D human breast cancer cells	2016	J Appl Toxicol. 2016 Jun;36(6):790-801. doi: 10.1002/jat.3210. Epub 2015 Aug 3.	Perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) are the two most popular surfactants among perfluorinated compounds (PFCs), with a wide range of uses. Growing evidence suggests that PFCs have the potential to interfere with estrogen homeostasis, posing a risk of endocrine-disrupting effects. This in vitro study aimed to investigate the estrogenic effect of these compounds on T47D hormone-dependent breast cancer cells. PFOS and PFOA (10(-12) to 10(-4) M) were not able to induce estrogen response element (ERE) activation in the ERE luciferase reporter assay. The ERE activation was induced when the cells were co-incubated with PFOS (10(-10) to 10(-7) M) or PFOA (10(-9) to 10(-7) M) and 1 nM of 17β-estradiol (E2). PFOS and PFOA did not modulate the expression of estrogen-responsive genes, including progesterone (PR) and trefoil factor (pS2), but these compounds enhanced the effect of E2-induced pS2 gene expression. Neither PFOS nor PFOA affected T47D cell viability at any of the tested concentrations. In contrast, co-exposure with PFOS or PFOA and E2 resulted in an increase of E2-induced cell viability, but no effect was found with 10 ng ml(-1) EGF co-exposure. Both compounds also intensified E2-dependent growth in the proliferation assay. ERK1/2 phosphorylation was increased by co-exposure with PFOS or PFOA and E2, but not with EGF. Collectively, this study shows that PFOS and PFOA did not possess estrogenic activity, but they enhanced the effects of E2 on estrogen-responsive gene expression, ERK1/2 activation and the growth of the hormone-deprived T47D cells. Copyright © 2015 John Wiley & Sons, Ltd.					●	●				-		B	A
1550	MOA（内分泌系）	Ishibashi, Hiroshi; Ishida, Haruna; Matsuoka, Munekazu; Tominaga, Nobuaki; Arizono, Koji	Estrogenic effects of fluorotelomer alcohols for human estrogen receptor isoforms alpha and beta in vitro	2007	Biol Pharm Bull. 2007 Jul;30(7):1358-9. doi: 10.1248/bpb.30.1358.	The present study demonstrates the estrogenic effects of fluorotelomer alcohols (FTOHs). In a yeast two-hybrid assay, treatment with 1H,1H,2H,2H-perfluorooctan-1-ol (6:2 FTOH), 1H,1H,2H,2H-perfluoro-decan-1-ol (8:2 FTOH) and 2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-nonadecafluoro-1-decanol (NFDH) showed a dose-dependent interaction between the human estrogen receptor (hER) isoforms hERalpha or hERbeta ligand-binding domain and coactivator TIF2, whereas there were no estrogenic effects of perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) for these hERs. The estrogenic effects of FTOHs on hERalpha were higher than those on hERbeta, indicating a differential responsiveness of hERs to FTOHs. The relative ranks of tested chemicals on the estrogenic effects for hERalpha and hERbeta descended in the order of estradiol-17beta>>>6:2 FTOH>NFDH>8:2 FTOH. These results suggest that certain FTOHs including 6:2 FTOH, 8:2 FTOH and NFDH interact with hER isoforms alpha and beta in vitro. Further studies are necessary to investigate contamination levels, potential biological effects and the risks of these compounds on human health.						●				-		D	C
1551	MOA（内分泌系）	Rosenmai, A K; Nielsen, F K; Pedersen, M; Hadrup, N; Trier, X; Christensen, J H; Vinggaard, A M	Fluorochemicals used in food packaging inhibit male sex hormone synthesis	2013	Toxicol Appl Pharmacol. 2013 Jan 1;266(1):132-42. doi: 10.1016/j.taap.2012.10.022. Epub 2012 Nov 7.	Polyfluoroalkyl phosphate surfactants (PAPS) are widely used in food contact materials (FCMs) of paper and board and have recently been detected in 57% of investigated materials. Human exposure occurs as PAPS have been measured in blood; however knowledge is lacking on the toxicology of PAPS. The aim of this study was to elucidate the effects of six fluorochemicals on sex hormone synthesis and androgen receptor (AR) activation in vitro. Four PAPS and two metabolites, perfluorooctanoic acid (PFOA) and 8:2 fluorotelomer alcohol (8:2 FTOH) were tested. Hormone profiles, including eight steroid hormones, generally showed that 8:2 diPAPS, 8:2 monoPAPS and 8:2 FTOH led to decreases in androgens (testosterone, dehydroepiandrosterone, and androstenedione) in the H295R steroidogenesis assay. Decreases were observed for progesterone and 17-OH-progesterone as well. These observations indicated that a step prior to progestagen and androgen synthesis had been affected. Gene expression analysis of StAR, Bzrp, CYP11A, CYP17, CYP21 and CYP19 mRNA showed a decrease in Bzrp mRNA levels for 8:2 monoPAPS and 8:2 FTOH indicating interference with cholesterol transport to the inner mitochondria. Cortisol, estrone and 17β-estradiol levels were in several cases increased with exposure. In accordance with these data CYP19 gene expression increased with 8:2 diPAPS, 8:2 monoPAPS and 8:2 FTOH exposures indicating that this is a contributing factor to the decreased androgen and the increased estrogen levels. Overall, these results demonstrate that fluorochemicals present in food packaging materials and their metabolites can affect steroidogenesis through decreased Bzrp and increased CYP19 gene expression leading to lower androgen and higher estrogen levels.						●				-		B	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報抽出対象	文献ランク①	文献ランク②
1552	実験動物（神経毒性）	Kawabata, K.; Matsuzaki, H.; Nukui, S.; Okazaki, M.; Sakai, A.; Kawashima, Y.; Kudo, N.	Perfluorododecanoic acid induces cognitive deficit in adult rats	2017	Toxicol Sci. 157: 421-428. doi: 10.1093/toxsci/kfx058.	The brain level of perfluorododecanoic acid (PFDoA) was compared with those of perfluorooctanoic acid (PFOA) and perfluorodecanoic acid (PFDA) in rats 9 days after a single oral dose (50 mg/kg). The PFDoA level in the brain was 44.0 ± 2.0 μg/g, which was higher than that in the serum (24.4 ± 1.0 μg/ml). In contrast, the concentrations of PFOA and PFDA in the brain were low (<0.8 and 4.7 ± 0.4 μg/g, respectively), and less than one-tenth of those in the serum. Next, to investigate the effects on brain function, the cognitive function alterations of PFOA, PFDA, and PFDoA were estimated by the novel object recognition test 5-6 days after dosing. A significant decrease in the discrimination index was observed in PFDoA-treated rats while no significant alteration was observed in PFDA- and PFOA-treated rats. The effects of PFDoA were further assessed by other behavioral tests. PFDoA-associated alteration was observed in the elevated-plus maze test, but not in the Y-maze test, open-field test, and forced swim test. A decrease in the discrimination index of the novel object recognition test was dependent on the PFDoA dose and the PFDoA concentration in the brain. PFDoA concentration in the brain was 28.6 ± 2.6 μg/g 30 days after dosing, and a decrease in discrimination index was observed. Taken together, these results suggest that PFDoA distributes in the brain easier than PFOA and PFDA and causes cognitive deficit.	●	●	●	●						-		B	B
1553	実験動物（神経毒性）	Long, Y.; Wang, Y.; Ji, G.; Yan, L.; Hu, F.; Gu, A.	Neurotoxicity of perfluorooctane sulfonate to hippocampal cells in adult mice	2013	PLoS ONE. 2013;8(1):e54176. doi: 10.1371/journal.pone.0054176. Epub 2013 Jan 30.	Perfluorooctane sulfonate (PFOS) is a ubiquitous pollutant and found in the environment and in biota. The neurotoxicity of PFOS has received much concern among its various toxic effects when given during developing period of brain. However, little is known about the neurotoxic effects and potential mechanisms of PFOS in the mature brain. Our study demonstrated the neurotoxicity and the potential mechanisms of PFOS in the hippocampus of adult mice for the first time. The impairments of spatial learning and memory were observed by water maze studies after exposure to PFOS for three months. Significant apoptosis was found in hippocampal cells after PFOS exposure, accompanied with a increase of glutamate in the hippocampus and decreases of dopamine (DA) and 3,4-dihydrophenylacetic acid (DOPAC) in Caudate Putamen in the 10.75 mg/kg PFOS group. By two-dimensional fluorescence difference in gel electrophoresis (2D-DIGE) analysis, seven related proteins in the hippocampus that responded to PFOS exposure were identified, among which, Mib1 protein (an E3 ubiquitin-protein ligase), Herc5 (hect domain and RLD 5 isoform 2) and Tyro3 (TYRO3 protein tyrosine kinase 3) were found down-regulated, while Sdha (Succinate dehydrogenase flavoprotein subunit), Gzma (Isoform HF1 of Granzyme A precursor), Plau (Urokinase-type plasminogen activator precursor) and Lig4 (DNA ligase 4) were found up-regulated in the 10.75 mg/kg PFOS-treated group compare with control group. Furthermore, we also found that (i) increased expression of caspase-3 protein and decreased expression of Bcl-2, Bcl-XL and survivin proteins, (ii) the increased glutamate release in the hippocampus. All these might contribute to the dysfunction of hippocampus which finally account for the impairments of spatial learning and memory in adult mice.	●	●		●	●		●		●	-	1	A	B
1554	in vitro（神経毒性）	Wang, Y.; Miao, Y.; Mir, A. Z.; Cheng, L.; Wang, L.; Zhao, L.; Cui, Q.; Zhao, W.; Wang, H.	Inhibition of beta-amyloid-induced neurotoxicity by pinocembrin through Nrf2/HO-1 pathway in SH-SY5Y cells	2016	J Neurol Sci. 368: 223-230. doi: 10.1016/j.jns.2016.07.010. Epub 2016 Jul 11.	Amyloid beta peptide (Aβ) can cause neurotoxicity in Alzheimer's disease (AD). It evokes a cascade of oxidative damage to neurons. Pinocembrin (PCB), the most abundant flavonoid in propolis, has been proven to have neuroprotective effects in vivo and in vitro. In the present study, we investigated the neuroprotective effects of PCB on Aβ25-35-induced neurotoxicity. Exposure of SH-SY5Y cells to 25μM Aβ25-35 for 24h caused viability loss, apoptotic increase and reactive oxygen species (ROS) increase, pre-treatment with PCB for 4h significantly reduced the viability loss, apoptotic rate and attenuated Aβ-mediated ROS production. PCB strikingly inhibited Aβ25-35-induced mitochondrial dysfunctions, including lowered membrane potential, decreased Bcl-2/Bax ratio. In addition, PCB suppressed the release of cytochrome c and the cleavage of caspase-3. PCB treatment also resulted in an increase in Nrf2 protein levels and subsequent induction of heme oxygenase-1(HO-1) expression in SH-SY5Y cells. RNA interference-mediated knockdown of Nrf2 expression suppressed the PCB-induced HO-1 expression. Notably, we found that the HO-1 inhibitor zinc protoporphyrin IX (ZnPP) markedly diminished the neuroprotective effect of PCB against Aβ-mediated neurotoxicity. Taken together, these results indicated that PCB protects SH-SY5Y cells from Aβ25-35-induced neurotoxicity through activation of Nrf2/HO-1 pathways. Thus, activation of Nrf2/HO-1 pathways and inhibition of mitochondria-dependent apoptosis together may protect cells from Aβ25-35-induceded neurotoxicity.	●	●								-		C	C
1555	実験動物（発達神経毒性）	Wang, Y.,u; Zhao, H.; Zhang, Q.; Liu, W.,ei; Quan, X.,ie	Perfluorooctane sulfonate induces apoptosis of hippocampal neurons in rat offspring associated with calcium overload	2015	Toxicology Research. 4: 931-938. doi: 10.1039/c4tx00177j	The purpose of this research is to investigate the effects of perfluorooctane sulfonate (PFOS) on neuronal apoptosis in the hippocampus of rat offspring, and to elucidate the underlying mechanisms associated with calcium homeostasis. A cross-fostering model was established, enabling the evaluation of prenatal and postnatal exposure. Internal exposure was measured via PFOS concentration analysis in serum and the hippocampus. Cell apoptosis of hippocampus neurons was identified together with the measurement of intracellular free calcium concentration ([Ca2+](i)). Continuous PFOS exposure in both the prenatal and postnatal period induced increasing apoptosis in hippocampus neurocytes. Meanwhile, [Ca2+](i) increased in a dose dependent manner in the continuous exposure groups and prenatal exposure groups. Furthermore, expression of apoptosis related genes can be used for the mechanistic analysis of the apoptotic effects induced by PFOS. Both apoptosis linked gene-2 (alg-2) and death-associated protein kinase (dapk2) genes were up-regulated, especially in the prenatal exposure groups on postnatal day (PND) 35 B-cell CLL/lymphoma (Bcl-2) was also significantly up-regulated both on PND7 and PND35. Overall results indicated that PFOS exposure caused increasing of apoptosis in the hippocampus, where [Ca2+](i) overload acted as a potential mechanism. Furthermore, prenatal exposure resulted in long-lasting effects on calcium homeostasis and the genes' expression regulated calcium signaling and apoptosis of rat offspring, highlighting the developmental neurotoxicity risk of fetal PFOS exposure.	●									-	1	A	D
1556	実験動物（発達神経毒性）	Zeng, H. C.; Zhang, L.; Li, Y. Y.; Wang, Y. J.; Xia, W.; Lin, Y.; Wei, J.; Xu, S. Q.	Inflammation-like glial response in rat brain induced by prenatal PFOS exposure	2011	Neurotoxicology. 2011 Jan;32(1):130-9. doi: 10.1016/j.neuro.2010.10.001. Epub 2010 Oct 19.	Numerous studies have indicated the neurotoxicity of perfluorooctane sulfonate (PFOS), a persistent and bioaccumulative compound, particularly during developmental stages of higher organisms. To explore the pro-inflammatory effect in the developmental neurotoxicity, effects of prenatal exposure to PFOS on glial activation in hippocampus and cortex were examined in offspring rats. Dams received 0.1, 0.6 and 2.0mg/kg bw PFOS by gavage from gestational day 2 (GD2) to GD21. Astrocyte activation markers, glial fibrillary acidic protein (GFAP) and S100 calcium binding protein B (S-100β) in hippocampus and cortex were both upregulated on postnatal day 0 (PND0) or PND21. In addition, the astrocyte activation was accompanied with the elevation of pro-inflammatory cytokines interleukin (IL-1β) and tumor necrosis factor (TNF)-α. The mRNA levels of pro-inflammatory transcription factors, including activation protein-1 (AP-1), nuclear factor-κB (NF-κB), and cAMP response element-binding protein (CREB) were also increased, at least in the 2.0mg/kg group. In addition to the inflammatory response, two synaptic proteins, synapsin 1 (Syn1) and synaptophysin (Syp) were reduced in cortex on PND0 and PND21. In hippocampus, the Syn1 were also reduced, while the Syp were increased in cortex on either PND0 or PND21. Obtained results indicated chronic glial activation with coexisting inflammatory and synapse injury features as a new mechanism of PFOS developmental neurotoxicity, and enhanced expression of AP-1, NF-κB and CREB may contributed to the adverse effect.	●	●		●						-	1	A	A
1557	実験動物（発達神経毒性）	Zhang, Q.; Liu, W.; Zhao, H.; Zhang, Z.; Qin, H.; Luo, F.; Niu, Q.	Developmental perfluorooctane sulfonate exposure inhibits long-term potentiation by affecting AMPA receptor trafficking	2019	Toxicology. 2019 Jan 15;412:55-62. doi: 10.1016/j.tox.2018.11.015. Epub 2018 Nov 30.	Both animal study and epidemiological survey revealed the associations between defects of cognitive function and the developmental exposure to perfluorooctane sulfonate (PFOS), while the mechanism is not well known. The SD rats were exposed PFOS at 1.7, 5 and 15 mg/L by drinking water from gestation to the adulthood of the pups for evaluating the effects of PFOS exposure on long-term potentiation (LTP) and the role of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors trafficking. Whole-life exposure of PFOS beginning in utero to adulthood significantly inhibited the induction and expression of LTP, and the input/output curve (I/O) and paired-pulse facilitation (PPF) were moderately suppressed, suggesting that PFOS might affect the synaptic transmission and plasticity both in pre- and post-synaptic cells. Meanwhile, PFOS decreased the mRNA levels of AMPA receptor subunits GluA1 and GluA2, and the protein amounts in the membrane, with the total GluA1 and GluA2 protein amounts increased, indicating the internalization of AMPA receptors. Furthermore, tests in the primary hippocampal neurons also support the decreased mRNA levels of GluA1 and GluA2 induced by PFOS. After the pretreatment of AMPA antagonist (NBQX), PFOS decreased the expression of GluA1 and GluA2 and increased internal cellular calcium at much lower levels than that in the neurons without NBQX treatment. The results provide electrophysiological evidence for the impaired cognitive function induced by PFOS exposure and revealed the critical role of AMPA receptor involved.	●	●								-	1	B	A
1558	in vitro（神経毒性）	Berntsen, Hanne Friis; Bjørklund, Cesilie Granum; Audinot, Jean-Nicolas; Hofer, Tim; Verhaegen, Steven; Lentzen, Esther; Gutleb, Arno Christian; Ropstad, Erik	Time dependent effects of perfluorinated compounds on viability in cerebellar granule neurons: dependence on carbon chain length and functional group attached	2017	Neurotoxicology. 2017 Dec;63:70-83. doi: 10.1016/j.neuro.2017.09.005. Epub 2017 Sep 15.	The toxicity of long chained perfluoroalkyl acids (PFAAs) has previously been reported to be related to the length of the perfluorinated carbon chain and functional group attached. In the present study, we compared the cytotoxicity of six PFAAs, using primary cultures of rat cerebellar granule neurons (CGNs). Two perfluoroalkyl sulfonic acids (PFSAs, chain length C(6) and C(8)) and four perfluoroalkyl carboxylic acids (PFCAs, chain length C(8)-C(11)) were studied. These PFAAs have been detected in human blood and the brain tissue of mammals. The cell viability trypan blue and MTT assays were used to determine toxicity potencies (based on LC(50) values) after 24h exposure (in descending order): perfluoroundecanoic acid (PFUnDA)≥perfluorodecanoic acid (PFDA)>perfluorooctanesulfonic acid potassium salt (PFOS)>perfluorononanoic acid (PFNA)>perfluorooctanoic acid (PFOA)>perfluorohexanesulfonic acid potassium salt (PFHxS). Concentrations of the six PFAAs that produced equipotent effects after 24h exposure were used to further explore the dynamics of viability changes during this period. Therefore viability was assessed at 10, 30, 60, 90, 120 and 180min as well as 6, 12, 18 and 24h. A difference in the onset of reduction in viability was observed, occurring relatively quickly (30-60min) for PFOS, PFDA and PFUnDA, and much slower (12-24h) for PFHxS, PFOA and PFNA. A slight protective effect of vitamin E against PFOA, PFNA and PFOS-induced reduction in viability indicated a possible involvement of oxidative stress. PFOA and PFOS did not induce lipid peroxidation on their own, but significantly accelerated cumene hydroperoxide-induced lipid peroxidation. When distribution of the six PFAAs in the CGN-membrane was investigated using NanoSIMS50 imaging, two distinct patterns appeared. Whereas PFHxS, PFOS and PFUnDA aggregated in large hotspots, PFOA, PFNA and PFDA showed a more dispersed distribution pattern. In conclusion, the toxicity of the investigated PFAAs increased with increasing carbon chain length. For molecules with a similar chain length, a sulfonate functional group led to greater toxicity than a carboxyl group.			●							-		B	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献リスト①	文献リスト②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1559	in vitro（神経毒性）	Berntsen, Hanne Friis; Bjø rklund, Cesilie Granum; Strandabø, Rønnaug; Haug, Trude Marie; Moldes-Anaya, Angel; Fuentes-Lazaro, Judit; Verhaegen, Steven; Paulsen, Ragnhild Elisabeth; Tasker, R Andrew; Ropstad, Erik	PFOS-induced excitotoxicity is dependent on Ca2+ influx via NMDA receptors in rat cerebellar granule neurons	2018	Toxicol Appl Pharmacol. 2018 Oct 15;357:19-32. doi: 10.1016/j.taap.2018.08.015. Epub 2018 Aug 23.	Perfluoroalkyl acids (PFAAs) are persistent compounds used in many industrial as well as consumer products. Despite restrictions, these compounds are found at measurable concentrations in samples of human and animal origin. In the present study we examined whether the effects on cell viability of two sulfonated and four carboxylated PFAAs in cultures of cerebellar granule neurons (CGNs), could be associated with deleterious activation of the N-methyl-d-aspartate receptor (NMDA-R). PFAA-induced effects on viability in rat CGNs and unstimulated PC12 cells were examined using the MTT assay. Cells from the PC12 rat pheochromocytoma cell line lack the expression of functional NMDA-Rs and were used to verify lower toxicity of perfluorooctanesulfonic acid (PFOS) in cells not expressing NMDA-Rs. Protective effects of NMDA-R antagonists, and extracellular as well as intracellular Ca(2+) chelators were investigated. Cytosolic Ca(2+) ([Ca(2+)](i)) was measured using Fura-2. In rat CGNs the effects of the NMDA-R antagonists MK-801, memantine and CPP indicated involvement of the NMDA-R in the decreased viability induced by PFOS and perfluorohexanesulfonic acid (PFHxS). No effects were associated with the four carboxylated PFAAs studied. Further, EGTA and CPP protected against PFOS-induced decreases in cell viability, whereas no protection was afforded by BAPTA-AM. [Ca(2+)](i) significantly increased after exposure to PFOS, and this increase was completely blocked by MK-801. In PC12 cells a higher concentration of PFOS was required to induce equivalent levels of toxicity as compared to in rat CGNs. PFOS-induced toxicity in PC12 cells was not affected by CPP. In conclusion, PFOS at the tested concentrations induces excitotoxicity in rat CGNs, which likely involves influx of extracellular Ca(2+) via the NMDA-R. This effect can be blocked by specific NMDA-R antagonists.			●							-		B	B
1560	実験動物（神経毒性）	Fuentes, Silvia; Vicens, Paloma; Colomina, M Teresa; Domingo, José L	Behavioral effects in adult mice exposed to perfluorooctane sulfonate (PFOS)	2007	Toxicology. 2007 Dec 5;242(1-3):123-9. doi: 10.1016/j.tox.2007.09.012. Epub 2007 Sep 16.	Nowadays, very little information concerning the effects on behavior in mammals of perfluorooctane sulfonate (PFOS), a widely distributed persistent environmental pollutant, is available. In the present study, we assessed the behavioral effects of PFOS on 3 months old mice after 1 month of exposure to this pollutant. Thirty adult mice were divided into three groups. Animals were given by gavage 0, 3, and 6 mg PFOS/kg/day for four consecutive weeks. After the treatment period, mice were evaluated for several skills by testing motor and sensory function by means of a functional observation battery (FOB), general activity and exploratory behavior in an open-field, and learning and memory in a water maze task. One week after behavioral testing, serum was collected for corticosterone analyses. No adverse effects were observed in the FOB. In general terms, activity in the open-field was similar in all groups being the only observed differences limited to the group given PFOS at 3mg/kg/day (spent less time in the center) and the group exposed to 6 mg PFOS/kg/day) (reduced rate of vertical activity). Concerning the effects of PFOS in the water maze, although all animals learned the task, no effect of the dose was observed during the acquisition. In the retention test, a deleterious effect of PFOS was noted. These results indicate that PFOS exposure induced only slight behavioral effects in adult male mice.				●	●					-	1	A	B
1561	実験動物（神経毒性）	Kawamoto, Kosuke; Sato, Itaru; Tsuda, Shuji; Yoshida, Midori; Yaegashi, Kaori; Saito, Norimitsu; Liu, Wei; Jin, Yihe	Ultrasonic-induced tonic convulsion in rats after subchronic exposure to perfluorooctane sulfonate (PFOS)	2011	J Toxicol Sci. 2011 Jan;36(1):55-62. doi: 10.2131/jts.36.55.	Perfluorooctane sulfonate (PFOS) is one of the persistent organic pollutants distributed widely in the global environment. We have found that a single oral administration of PFOS induced tonic convulsion in mice and rats when a brief ultrasonic stimulus was applied to the animals. The aim of this study is to examine whether the neurotoxicity is caused by subchronic dietary exposure to PFOS. Rats were treated with dietary PFOS at 0, 2, 8, 32 and 128 ppm for 13 weeks. Animals were carefully observed for pharmacotoxic signs and responses to the ultrasonic stimulus applied biweekly. PFOS increased liver weight and decreased food consumption and body weight. PFOS concentrations in the serum, brain, liver and kidney were increased almost proportional to its total dose, although the ratios of PFOS concentrations in tissues to total doses in the group treated with the highest concentration were a little lower. The ranges of relative concentrations in the brain, liver and kidney to serum concentration were 0.13 to 0.24, 2.7 to 6.3 and 0.82 to 1.6, respectively. PFOS alone did not cause any neurotoxic symptoms; however, 5 rats out of 6 showed tonic convulsion in the 6th week when ultrasonic stimulus was applied to the 128 ppm rats with the total PFOS dose of 338 mg/kg. The ultrasonic stimulus did not cause convulsion in the other groups. Histopathological examination including electron microscopic examination could not detect any abnormality in the brain. Because the acute oral dose of PFOS causing the convulsion was 250 mg/kg (Sato et al., 2009), the convulsion induced by PFOS seemed to depend on its total dose regardless of treatment schedule.				●	●				●	-	1	A	B
1562	実験動物（内分泌系）	López-Doval, S; Salgado, R; Pereiro, N; Moyano, R; Lafuente, A	Perfluorooctane sulfonate effects on the reproductive axis in adult male rats	2014	Environ Res. 2014 Oct;134:158-68. doi: 10.1016/j.envres.2014.07.006. Epub 2014 Aug 27.	Perfluorooctane sulfonate (PFOS) is a neurotoxic agent and it can disrupt the endocrine system activity. This work was undertaken to evaluate the possible effects of PFOS exposure on the hypothalamic-pituitary-testicular axis (HPT) in adult male rats, and to evaluate the possible morphological alterations induced by PFOS in the endocrine tissues of this axis. Adult male rats were orally treated with 0.5; 1.0; 3.0 and 6.0 mg of PFOS/kg/day for 28 days. After PFOS exposure, hypothalamic noradrenaline concentration increased in the anterior hypothalamus and in the median eminence, not changing in the mediobasal hypothalamus. PFOS treated rats presented a decrease of the gonadotropin releasing hormone (GnRH) gene expression, increasing the mRNA levels of the luteinizing hormone (LH) in rats treated with all doses administered except with the dose of 6 mg/kg/day. PFOS also induced a raise of the follicle stimulating hormone (FSH) gene expression in the animals exposed to 0.5 and 1.0 mg of PFOS/kg/day. After PFOS exposure, hypothalamic GnRH concentration was modified, LH and testosterone release was inhibited and FSH secretion was stimulated. Moreover, PFOS induced several histopathological alterations in the hypothalamus, pituitary gland and testis. The results obtained in the present study suggest in general terms that PFOS can inhibit the physiological activity of the reproductive axis in adult male rats, which could be explained, at least in part, by the structural alterations showed in the animals exposed to this chemical: very dense chromatin, condensed ribosomes and a loss of the morphology in the hypothalamus; a degeneration of the gonadotrophic cells, as well as a loss and degeneration of the spermatozoids and a very marked edema in the testis.					●					-	1	B	A
1563	実験動物（神経毒性）	Sato, Itaru; Kawamoto, Kosuke; Nishikawa, Yasuo; Tsuda, Shuji; Yoshida, Midori; Yaegashi, Kaori; Saito, Norimitsu; Liu, Wei; Jin, Yihe	Neurotoxicity of perfluorooctane sulfonate (PFOS) in rats and mice after single oral exposure	2009	J Toxicol Sci. 2009 Oct;34(5):569-74. doi: 10.2131/jts.34.569.	Perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) are widely used in industrial fields and consumer products, and are ubiquitously found in the environment and animal tissues. In the present study, their neurotoxicity was examined using rats and mice by means of neurobehavioral observation, histopathological inspection and chemical assays. PFOS and PFOA alone did not cause any neurotoxic symptoms up to their sublethal doses (PFOS: 500 mg/kg, PFOA: 1,000 mg/kg). However, tonic convulsions were caused in the PFOS-treated rats (> or = 250 mg/kg) and mice (> or = 125 mg/kg) when ultrasonic stimulus was applied to the animals. The same ultrasonic stimulus never induced convulsions in the control animals and in the animals treated with PFOA. Concentration of PFOS in the brain was considerably lower than in other tissue, but it seemed to increase gradually with time after exposure. No morphological changes were detected by histopathological examination of the brain. There were also no changes in concentrations of norepinephrine, dopamine, serotonin, glycine, 4-aminobutylic acid and glutamic acid in the brain. The present study revealed neurotoxic effects of PFOS in animals. Convulsive effect of PFOS may not be attributed to the quantitative alterations of neurotransmitters or lesions of nerve cells in the brain, although the mechanism of its neurotoxicity has not been cleared.					●	●				-		B	B
1564	実験動物（神経毒性）	Yu, Y; Wang, C; Zhang, X; Zhu, J; Wang, L; Ji, M; Zhang, Z; Ji, XM; Wang, SL.	Perfluorooctane sulfonate disrupts the blood brain barrier through the crosstalk between endothelial cells and astrocytes in mice	2019	Environ Pollut. 2020 Jan;256:113429. doi: 10.1016/j.envpol.2019.113429. Epub 2019 Oct 24.	Perfluorooctane sulfonate (PFOS), a classic environmental pollutant, is reported to accumulate in brain and induce neurotoxicity. However, little is known the route and mechanism of its entrance in brain. In the present study, ICR mice were treated with PFOS for 28 days, the cerebral PFOS were measured and the morphological and ultrastructural changes of blood-brain barrier (BBB) were observed. Also, the expression and localization of the proteins related to the cerebral damages, tight junctions (TJs) and p38 activation were detected. Additionally, U87 cells were used to explore the role of p38 in PFOS-induced damages of astrocytes. PFOS significantly decreased the expression of TJ-related proteins (ZO-1, Claudin-5, Claudin-11, Occludin) in endothelial cells and disrupted BBB, which subsequently led PFOS to astrocytes and increased the expression of the proteins related to astrocytic damages (Aquaporin 4 and S100β). These results aggravated BBB disruption and further increased the cerebral PFOS levels. Besides, phosphorylated p38 activation was involved into PFOS-induced astrocytic damages in vivo and in vitro. In conclusion, the crosstalk between endothelial cells and astrocytes facilitated the BBB disruption and increased the accumulation of PFOS in brain. Our findings provided a new insight into the toxicological and physiological profiles of PFOS-induced neurotoxicity.		●								-	1	A	B
1565	実験動物（神経毒性）	Liu, Xiaohui; Liu, Wei; Jin, Yihe; Yu, Wenguang; Liu, Li; Yu, Hongyao	Effects of subchronic perfluorooctane sulfonate exposure of rats on calcium-dependent signaling molecules in the brain tissue	2010	Arch Toxicol. 2010 Jun;84(6):471-9. doi: 10.1007/s00204-010-0517-9. Epub 2010 Feb 2.	Perfluorooctane sulfonate (PFOS) is a persistent and bio-accumulative pollutant ubiquitous in wildlife and humans, which receives many concerns on the fate, transport, distribution, and toxicity. Studies have shown that PFOS-induced neurotoxicity in experimental animals; however, little is known about the potential mechanism of PFOS exposure on the central nervous system (CNS). Ca(2+)/calmodulin-dependent protein kinase IIalpha (CaMKIIalpha), cAMP-response element binding protein (CREB), c-fos, and c-jun, which are important down-stream molecules of calcium signaling in describing neuron cells structure and function in the CNS, were examined in the paper with the purpose to evaluate the effect of PFOS exposure on brain and approach the molecular mechanisms involved in the neurotoxicity induced by PFOS. Adult male Sprague-Dawley rats were administered with PFOS at dosages of 1.7, 5.0, and 15.0 mg/L in drinking water for 91 consecutive days. LC/MS was used for PFOS analysis in brain tissues, and western blot was employed to determine the expression of CaMKIIalpha and pCREB in the isolated cortex and hippocampus. The expression of c-fos and c-jun was detected by real-time reverse transcription polymerase chain reaction. The results showed that the expression of CaMKIIalpha and pCREB exhibits a significant increase in cortex and hippocampus after treatment with PFOS, compared with the control. The transcription factor c-fos was up-regulated in hippocampus, and c-jun was elevated both in cortex and hippocampus in PFOS-treated groups. These results indicated that, at least in part, the neurotoxic effect induced by PFOS is mediated by the Ca(2+)-dependent molecules in calcium signaling.					●					-	1	A	B
1566	実験動物（反復投与毒性）	Goldenthal, E; Jessup, DC; Geil, RG; Mehring, JS.	Ninety-day subacute rhesus monkey toxicity study: Fluorad ¨ Fluorochemical FC-143 (Study No. 137-090)	1978	St. Paul, MN: Report prepared for 3M by Institutional Research and Devlopment Corporation (Mattawan, MN).	No abstract available	●	●							企業データ		D	D

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1567	実験動物（消化管毒性）	Chang, S.; Parker, G. A.; Kleinschmidt, S. E.; Olsen, G. W.; Ley, C. A.; Taiwo, O. A.	A Pathology Review of the Lower Gastrointestinal Tract in Relation to Ulcerative Colitis in Rats and Cynomolgus Macaques Treated With Ammonium Perfluorooctanoate	2020	Toxicol Pathol. 2020 Jun;48(4):593-602. doi: 10.1177/0192623320911606. Epub 2020 Mar 18.	Among many short-term, subchronic, and chronic toxicology studies with ammonium perfluorooctanoate (PFOA), the gastrointestinal tract has not been identified as a target organ for PFOA-related toxicity in laboratory animals where the corresponding serum PFOA concentrations typically approach several orders of magnitude higher than the general human population. These lack of gastrointestinal tract-related findings were in direct contrast to an epidemiological observation where a positive trend was observed for ulcerative colitis, an idiopathic chronic inflammatory condition of the gut, in a Mid-Ohio River community whose drinking water contained higher levels of PFOA. This study was conducted to perform a histological reevaluation of large intestine sections in laboratory animals from 2 long-term toxicological studies: one was with Sprague Dawley rats that received ammonium PFOA in their diet for 2 years and the other one was with cynomolgus macaques that received daily capsules of ammonium PFOA for 6 months. In both studies, there was a lack of histological evidence of treatment-related inflammatory lesions that was suggestive of the occurrence of ulcerative colitis in these laboratory animals even under the most rigorous treatment schedules. These findings do not offer support for the biological plausibility of the epidemiological associations reported.	●	●							総説		D	C
1568	in vitro（肝毒性）	Wielsøe, Maria; Long, Manhai; Ghisari, Mandana; Bonefeld-Jørgensen, Eva C	Perfluoroalkylated substances (PFAS) affect oxidative stress biomarkers in vitro	2015	Chemosphere. 2015 Jun;129:239-45. doi: 10.1016/j.chemosphere.2014.10.014. Epub 2014 Nov 12.	Perfluoroalkylated substances (PFAS) have been widely used since 1950s and humans are exposed through food, drinking water, consumer products, dust, etc. The long-chained PFAS are persistent in the environment and accumulate in wildlife and humans. They are suspected carcinogens and a potential mode of action is through generation of oxidative stress. Seven long-chained PFAS found in human serum were investigated for the potential to generate reactive oxygen species (ROS), induce DNA damage and disturb the total antioxidant capacity (TAC). The tested PFAS were perfluorohexane sulfonate (PFHxS), perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoate (PFNA), perfluorodecanoate (PFDA), perfluoroundecanoate (PFUnA), and perfluorododecanoate (PFDoA). Using the human hepatoma cell line (HepG2) and an exposure time of 24h we found that all three endpoints were affected by one or more of the compounds. PFHxS, PFOA, PFOS and PFNA showed a dose dependent increase in DNA damage in the concentration range from 2×10(-7) to 2×10(-5)M determined by the comet assay. Except for PFDoA, all the other PFAS increased ROS generation significantly. For PFHxS and PFUnA the observed ROS increases were dose-dependent. Cells exposed to PFOA were found to have a significant lower TAC compared with the solvent control, whereas a non-significant trend in TAC decrease was observed for PFOS and PFDoA and an increase tendency for PFHxS, PFNA and PFUnA. Our results indicate a possible genotoxic and cytotoxic potential of the PFAS in human liver cells.			●					●	-	1	A	A
1569	実験動物（その他）	Feng, Yixing; Shi, Zhimin; Fang, Xuemei; Xu, Muqi; Dai, Jiayin	Perfluorononanoic acid induces apoptosis involving the Fas death receptor signaling pathway in rat testis	2009	Toxicol Lett. 2009 Oct 28;190(2):224-30. doi: 10.1016/j.toxlet.2009.07.020. Epub 2009 Jul 29.	Perfluorononanoic acid (PFNA, C9), a synthetic perfluorinated chemical containing nine carbons, accumulates and is biomagnified through food webs. This compound has been detected in the serum of humans and wildlife and has the potential for reproductive interference. Few studies, however, have reported the effects of PFNA exposure on male reproduction. To determine this, male rats were orally dosed for 1, 3 and 5mg/kgday PFNA or with vehicle for 14 days. In the present study, serum testosterone levels were decreased, while estradiol levels were increased dramatically in rats receiving 5mg PFNA/kgday. Spermatogenic cells from rats that received 5mg PFNA/kgday exhibited apoptotic features including crescent chromatin condensation and chromatin margination. Flow cytometric analysis and TUNEL assays revealed a dose-dependent increase of apoptotic cell numbers. In addition, expression of Fas and Bax mRNA levels were upregulated significantly, and Bcl-2 mRNA levels were downregulated markedly in the 3 and 5mg/kgday groups. A dose-dependent increase in levels of active caspase-8 and no significant changes of active caspase-9 were observed. Our results indicate that PFNA exposure can lead to cell apoptosis in rat testis, and this apoptosis was probably associated with the Fas death receptor-dependent apoptotic pathway.				●					-		B	C
1570	実験動物（肝毒性）	Guruge, Keerthi S; Yeung, Leo W Y; Yamanaka, Noriko; Miyazaki, Shigeru; Lam, Paul K S; Giesy, John P; Jones, Paul D; Yamashita, Nobuyoshi	Gene expression profiles in rat liver treated with perfluorooctanoic acid (PFOA)	2006	Toxicol Sci. 2006 Jan;89(1):93-107. doi: 10.1093/toxsci/kfj011. Epub 2005 Oct 12.	Perfluorooctanoic acid (PFOA; Pentadecafluorooctanoic acid) is widely used in various industrial applications. It is persistent in the environment and does not appear to undergo further degradation or transformation. PFOA is found in tissues including blood of wildlife and humans; however, the environmental fate and biological effects of PFOA remain unclear. Microarray techniques of gene expression have become a powerful approach for exploring the biological effects of chemicals. Here, the Affymetrix, Inc. rat genome 230 2.0 GeneChip was used to identify alterations in gene regulation in Sprague-Dawley rats treated with five different concentrations of PFOA. Male rats were exposed by daily gavage to 1, 3, 5, 10, or 15 mg PFOA/kg, body weight (bw)/day for 21 days and at the end of the exposure, liver was isolated and total liver RNA were used for the gene chip analysis. Over 500 genes, whose expression was significantly ($p < 0.0025$) altered by PFOA at two-fold changes compared to control, were examined. The effects were dose-dependent with exposure to 10 mg PFOA/kg, bw/day, causing alteration in expression of the greatest number of genes (over 800). Approximately 106 genes and 38 genes were consistently up- or down-regulated, respectively, in all treatment groups. The largest categories of induced genes were those involved in transport and metabolism of lipids, particularly fatty acids. Other induced genes were involved in cell communication, adhesion, growth, apoptosis, hormone regulatory pathways, proteolysis and peptidolysis and signal transduction. The genes expression of which was suppressed were related to transport of lipids, inflammation and immunity, and especially cell adhesion. Several other genes involved in apoptosis; regulation of hormones; metabolism; and G-protein coupled receptor protein signaling pathways were significantly suppressed.				●					遺伝子発現解析→実験動物	1	B	A
1571	実験動物（その他）	Loveless, Scott E; Finlay, Carol; Everds, Nancy E; Frame, Steven R; Gillies, Peter J; O'Connor, John C; Powley, Charles R; Kennedy, Gerald L	Comparative responses of rats and mice exposed to linear/branched, linear, or branched ammonium perfluorooctanoate (APFO)	2006	Toxicology. 2006 Mar 15;220(2-3):203-17. doi: 10.1016/j.tox.2006.01.003. Epub 2006 Jan 31.	The purpose of this study was to compare the toxicity of linear/branched ammonium perfluorooctanoate (APFO) with that of linear and branched APFO. Linear/branched APFO (approximately 80% linear and 20% branched isomers) was formerly used in the production of commercial products. The extensive toxicologic database for APFO has been developed essentially using this mixture of isomers. The trend now is to use APFO containing only the linear isomer. The current study was performed to determine if the toxicological database developed for the linear/branched isomer is applicable to the linear isomer. To determine the contribution of branched APFO to the toxicity of linear/branched APFO, a form of APFO that was 100% branched was synthesized. Rats and mice were given doses by oral gavage ranging from 0.3 to 30 mg/kg of either the linear/branched, linear, or branched APFO for 14 days. Clinical signs, body weights, food consumption, selected hematology and serum lipid parameters, liver and kidney weights, hepatic peroxisomal beta-oxidation, and serum PFOA concentrations were evaluated. Mean body weights were about 20% lower in rats and mice dosed with 30 mg/kg of linear/branched or linear APFO compared to controls, and 3-5% lower in animals dosed with 30 mg/kg of branched APFO. In rats, all three forms reduced lipids. In mice, all three forms reduced total and HDL cholesterol similarly but triglycerides were increased at lower doses. Increased peroxisomal beta-oxidation activity and serum PFOA concentrations were seen in both species but these effects were least pronounced in rats dosed with the branched material. In rats, serum PFOA levels were 20-51 ppm at Lowest Observed Effect Levels (LOEL) of 0.3-1 mg/kg, based primarily upon lipid parameters. In mice, serum PFOA levels were 10-14 ppm at the LOEL of 0.3 mg/kg, based primarily upon relative liver weight. In both rats and mice, the overall responses to the linear/branched and the linear forms of PFOA were similar, but the branched form appears to be less potent. Based on these results, and for the endpoints evaluated in this study, the toxicological database developed primarily from testing linear/branched APFO is applicable to linear APFO.				●		●			-		B	B
1572	実験動物（その他）	Upham, B L; Deocampo, N D; Wurl, B; Trosko, J E	Inhibition of gap junctional intercellular communication by perfluorinated fatty acids is dependent on the chain length of the fluorinated tail	1998	Int J Cancer. 1998 Nov 9;78(4):491-5. doi: 10.1002/(sici)1097-0215(19981109)78:4<491::aid-ijc16>3.0.co;2-9.	Perfluorinated fatty acids (PFFAs), such as perfluorooctanoic acid (PFOA) and perfluorodecanoic acid (PFDA), are known peroxisome proliferators and hepatocarcinogens. A causal link between an increase in the oxidative stress by peroxisomes and tumor promotion has been proposed to explain the hepatocarcinogenicity of PFOA and PFDA. However, the down-regulation of gap junctional intercellular communication (GJIC) has also been linked to the tumor-promoting properties of many carcinogens. Therefore, the effect of PFFAs on GJIC in WB-rat liver epithelial cells was determined. The chain length of the PFFAs tested for an effect on GJIC ranged from 2 to 10, 16 and 18 carbons. Carbon lengths of 7 to 10 inhibited GJIC in a dose-response fashion, whereas carbon lengths of 2 to 5, 16 and 18 did not appreciably inhibit GJIC. Inhibition occurred within 15 min and was reversible, with total recovery from inhibition occurring within 30 min after the removal of the compound from the growth medium. This short time of inhibition suggests that GJIC was modified at the post-translational level. Also, this short time period was not long enough for peroxisome proliferation. The post-translational modification of the gap junction proteins was not a consequence of altered phosphorylation as determined by Western blot analysis. Perfluorooctanesulfonic acid also inhibited GJIC in a dose-response fashion similar to PFDA, indicating that the determining factor of inhibition was probably the fluorinated tail, which required 7-10 carbons. Our results suggest that PFFAs could potentially act as hepatocarcinogens at the level of gap junctions in addition to or instead of through peroxisome proliferation.				●					-		C	D
1573	実験動物（その他）	Upham, Brad L; Park, Joon-Suk; Babica, Pavel; Sovadinova, Iva; Rummel, Alisa M; Trosko, James E; Hirose, Akihiko; Hasegawa, Ryuichi; Kanno, Jun; Sai, Kimie	Structure-activity-dependent regulation of cell communication by perfluorinated fatty acids using in vivo and in vitro model systems	2009	Environ Health Perspect. 2009 Apr;117(4):545-51. doi: 10.1289/ehp.11728. Epub 2008 Oct 23.	BACKGROUND: Perfluoroalkanoates, [e.g., perfluorooctanoate (PFOA)], are known peroxisome proliferators that induce hepatomegaly and hepatocarcinogenesis in rodents, and are classic non-genotoxic carcinogens that inhibit in vitro gap-junctional intercellular communication (GJIC). This inhibition of GJIC is known to be a function of perfluorinated carbon lengths ranging from 7 to 10. OBJECTIVES: The aim of this study was to determine if the inhibition of GJIC by PFOA but not perfluoropentanoate (PFPeA) observed in F344 rat liver cells in vitro also occurs in F344 rats in vivo and to determine mechanisms of PFOA dysregulation of GJIC using in vitro assay systems. METHODS: We used an incision load/dye transfer technique to assess GJIC in livers of rats exposed to PFOA and PFPeA. We used in vitro assays with inhibitors of cell signaling enzymes and antioxidants known to regulate GJIC to identify which enzymes regulated PFOA-induced inhibition of GJIC. RESULTS: PFOA inhibited GJIC and induced hepatomegaly in rat livers, whereas PFPeA had no effect on either end point. Serum biochemistry of liver enzymes indicated no cytotoxic response to these compounds. In vitro analysis of mitogen-activated protein kinase (MAPK) indicated that PFOA, but not PFPeA, can activate the extracellular receptor kinase (ERK). Inhibition of GJIC, in vitro, by PFOA depended on the activation of both ERK and phosphatidylcholine-specific phospholipase C (PC-PLC) in the dysregulation of GJIC in an oxidative-dependent mechanism. CONCLUSIONS: The in vitro analysis of GJIC, an epigenetic marker of tumor promoters, can also predict the in vivo activity of PFOA, which dysregulated GJIC via ERK and PC-PLC.				●					-		C	B

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①抽出	文献クラン②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1574	MOA（肝毒性）	Hu, X. Z.; Hu, D. C.	Effects of perfluorooctanoate and perfluorooctane sulfonate exposure on hepatoma Hep G2 cells	2009	Arch. Toxicol., 83: 851–861. doi: 10.1007/s00204-009-0441-z. Epub 2009 May 27.	Perfluorinated compounds (PFCs) are emerging compounds of concern. They are widely distributed in the environment, wildlife and human. Concern has been raised over their possible adverse effects on human health. This study was designed to determine cytotoxic effects of two important PFCs, perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS), in a single and a mixture of them exposure to Hep G2 cells. The results showed that PFOA and PFOS (50-200 micromol/l) induced production of reactive oxygen species (ROS), dissipation of mitochondria membrane potential and apoptosis of Hep G2 cells. Moreover, activities of superoxide dismutase, catalase and glutathione reductase were increased, whereas activities of glutathione-S-transferase and glutathione peroxidase were decreased. Glutathione content was reduced. Differential expression of genes, such as p53, Bcl-2, caspase-9, was evident in PFOA or PFOS exposure groups. The possible mechanism was that they could overwhelm homeostasis of antioxidative systems, boost ROS generation, impact mitochondria, and affect genes expression of apoptotic regulators, which resulted in start-ups of apoptosis program. Cells exposed to mixture of PFOA and PFOS and each of them showed non-apoptotic rate significant difference, which indicated that the combined effect of two compounds was summation effect, but neither synergistic nor antagonistic effect.					●	●				-		B	A
1575	MOA	Meek, M E Bette; Palermo, Christine M; Bachman, Ammie N; North, Colin M; Jeffrey Lewis, R	Mode of action human relevance (species concordance) framework: Evolution of the Bradford Hill considerations and comparative analysis of weight of evidence	2014	J Appl Toxicol. 2014 Jun;34(6):595-606. doi: 10.1002/jat.2984. Epub 2014 Feb 10.	The mode of action human relevance (MOA/HR) framework increases transparency in systematically considering data on MOA for end (adverse) effects and their relevance to humans. This framework continues to evolve as experience increases in its application. Though the MOA/HR framework is not designed to address the question of "how much information is enough" to support a hypothesized MOA in animals or its relevance to humans, its organizing construct has potential value in considering relative weight of evidence (WOE) among different cases and hypothesized MOA(s). This context is explored based on MOA analyses in published assessments to illustrate the relative extent of supporting data and their implications for dose-response analysis and involved comparisons for chemical assessments on trichloropropane, and carbon tetrachloride with several hypothesized MOA(s) for cancer. The WOE for each hypothesized MOA was summarized in narrative tables based on comparison and contrast of the extent and nature of the supporting database versus potentially inconsistent or missing information. The comparison was based on evolved Bradford Hill considerations rank ordered to reflect their relative contribution to WOE determinations of MOA taking into account increasing experience in their application internationally. This clarification of considerations for WOE determinations as a basis for comparative analysis is anticipated to contribute to increasing consistency in the application of MOA/HR analysis and potentially, transparency in separating science judgment from public policy considerations in regulatory risk assessment.					●	●				-		D	C
1576	遺伝毒性	Crebelli, R.; Caiola, S.; Conti, L.; Cordelli, E.; De Luca, G.; Dellatte, E.; Eleuteri, P.; Iacovella, N.; Leopardi, P.; Marcon, F.; Sanchez, M.; Sestili, P.; Siniscalchi, E.; Villani, P.	Can sustained exposure to PFAS trigger a genotoxic response? A comprehensive genotoxicity assessment in mice after subacute oral administration of PFOA and PFBA	2019	Regul Toxicol Pharmacol. 2019 Aug;106:169-177. doi: 10.1016/j.yrtph.2019.05.005. Epub 2019 May 7.	PFAS (perfluoroalkyl substances) are considered non-genotoxic. However, PFAS exposure has been associated with the induction of oxidative stress in vitro and in vivo, and the possible induction of indirect genotoxic effects under sustained PFAS exposure has not been investigated. In order to shed light on this aspect, in this study a comprehensive assessment of genotoxicity was carried out in mice administered with perfluorooctanoic acid (PFOA, 0.1, 1 and 5 mg/kg body weight) and its C4 analogue perfluorobutyric acid (PFBA, 5 mg/kg body weight) for five weeks through drinking water. Markers of cell toxicity, oxidative stress and DNA strand breaks were measured in liver, the main target of toxicity of PFOA in rodents; systemic genotoxicity was also assessed by the analysis of micronuclei in reticulocytes and spleen lymphocytes, and germ cell effects by the Comet assay on testis cells. PFOA administration at the highest dose (5 mg/kg body weight) induced marked liver hypertrophy with signs of cell injury (elevated ALT and AST), with no concurrent evidence of lipid peroxidation and oxidative stress (decreased antioxidant capacity). Only mild liver hypertrophy, with no other signs of toxicity, was determined by PFBA administration. No evidence of treatment related genotoxicity was observed in any experimental group. Overall, data indicate that under the experimental conditions of this study, severe liver toxicity induced by PFOA administration is not associated with oxidative stress. Accordingly, no genotoxic effect is observed in liver and in the other tissues examined. Milder evidence of liver toxicity, with no genotoxicity, and a lower tendency to bioaccumulation were observed in PFBA treated mice.	●	●	●							-	1	A	-
1577	遺伝毒性	Rashid, V. A.; Ahmad, S.; Irudayaraj, J. M. K.	Effect of Perfluorooctanoic Acid on the Epigenetic and Tight Junction Genes of the Mouse Intestine	2020	Toxics. 2020 Aug 28;8(3):64. doi: 10.3390/toxics8030064.	Perfluorooctanoic acid (PFOA) has been implicated in various toxicities including neurotoxicity, genotoxicity, nephrotoxicity, epigenetic toxicity, immunotoxicity, reproductive toxicity, and hepatotoxicity. However, information on the accumulation of PFOA in the intestine and its toxic effects on intestinal epigenetics and tight junction (TJ) genes is sparse. CD1 mice were dosed with PFOA (1, 5, 10, or 20 mg/kg/day) for 10 days, and its accumulation and induced alterations in the expression of epigenetic and tight junction genes in the small intestine and colon were evaluated using LC-MS and qPCR techniques. PFOA reduced the expression levels of DNA methyltransferases (Dnmt1, Dnmt3a, Dnmt3b) primarily in the small intestine whereas, in the colon, a decrease was observed only at high concentrations. Moreover, ten-eleven translocation genes (Tet2 and Tet3) expression was dysregulated in the small intestine, whereas in the colon Tets remained unaffected. The tight junction genes Claudins (Cldn), Occludin (Ocln), and Tight Junction Protein (Tjp) were also heavily altered in the small intestine. TJs responded differently across the gut, in proportion to PFOA dosing. Our study reveals that PFOA triggers DNA methylation changes and alters the expression of genes essential for maintaining the physical barrier of intestine, with more profound effects in the small intestine compared to the colon.	●	●								-		C	-
1578	遺伝毒性	van den Dungen, M. W.; Murk, A. J.; Kampman, E.; Steegenga, W. T.; Kok, D. E.	Association between DNA methylation profiles in leukocytes and serum levels of persistent organic pollutants in Dutch men	2017	Environ Epigenet. 3: dvx001. doi: 10.1093/eep/dvx001. eCollection 2017 Jan.	Consumption of polluted fish may lead to high levels of persistent organic pollutants (POPs) in humans, potentially causing adverse health effects. Altered DNA methylation has been suggested as a possible contributor to a variety of adverse health effects. The aim of this study was to evaluate the relationship between serum POP levels (dioxins, polychlorobiphenyls, and perfluorooctane sulphonate) and DNA methylation. We recruited a total of 80 Dutch men who regularly consumed eel from either low- or high-polluted areas, and subsequently had normal or elevated POP levels. Clinical parameters related to e.g. hormone levels and liver enzymes were measured as biomarkers for adverse health effects. The Infinium 450K BeadChip was used to assess DNA methylation in a representative subset of 34 men. We identified multiple genes with differentially methylated regions (DMRs; FALSE discovery rate <0.05) related to POP levels. Several of these genes are involved in carcinogenesis (e.g. BRCA1, MAGEE2, HOXA5), the immune system (e.g. RNF39, HLA-DQB1), retinol homeostasis (DHRS4L2), or in metabolism (CYP1A1). The DMRs in these genes show mean methylation differences up to 0.074 when comparing low- and high-exposed men, with a mean difference up to 0.144 for single positions within a DMR. Clinical parameters were not significantly associated with serum POP levels. This is the first explorative study investigating extensive DNA methylation in relation to serum POP levels among men. We observed that elevated POP levels are associated with aberrant DNA methylation profiles in adult men who consumed high-polluted eel. These preliminary findings warrant further confirmation in other populations.	●	●								-		C	-
1579	遺伝毒性	Ayanda I, Min Y, Yu Z and Zha J,	Cytotoxic and genotoxic effects of perfluorododecanoic acid (PFDoA) in Japanese medaka	2018	Knowledge and Management of Aquatic Ecosystems, 419, 7 pp. doi: 0.1051/kmae/2017058	This study investigated the cytotoxic and genotoxic potential of perfluorododecanoic acid (PFDoA), a perfluorinated carboxylic chemical (PFC) that has broad applications and distribution in the environment in Japanese medaka, Oryzias latipes. Micronucleus (MN) test and Comet assay were used for the toxicity study. Three groups of fish were exposed to 0.1 mg/L, 0.5 mg/L and 2.5 mg/L concentration of the chemical for 28 days. Another group served as control. Sampling of the fish blood and liver were done after days 1, 4, 7, 14, 21 and 28 for analysis of different erythrocyte abnormalities and damage to DNA using the MN test and Comet assay respectively. Results showed that there was a significant time and concentration dependent increase ($p < 0.05$) in percent tail length of DNA and frequency of erythrocyte abnormalities. Nuclear abnormalities observed include micronucleus, fragmented apoptotic cells, lobed nuclei, and bean-shaped cells. Increase in induction of erythrocyte abnormalities and percent tail length of DNA peaked at days 14 and 7, respectively, after which there was a gradual decline. The results indicate that sub-chronic exposure of PFDoA to Japanese medaka caused DNA damage with a simultaneous induction of different erythrocyte abnormalities.										-		C	-
1580	遺伝毒性	Chen, Yuanhong; Hu, Wei; Huang, Changjiang; Hua, Shushan; Wei, Qihao; Bai, Chenglian; Chen, Jiangfei; Norris, Michelle B; Winn, Richard; Yang, Dongren; Dong, Qiaoxiang	Subchronic perfluorooctanesulfonate (PFOS) exposure induces elevated mutant frequency in an in vivo k transgenic medaka mutation assay	2016	Sci Rep. 2016 Dec 8;6:38466. doi: 10.1038/srep38466.	Perfluorooctanesulfonate (PFOS) has been widely detected in the environment, wildlife and humans, but few studies have ever examined its mutagenic effect in vivo. In the present study, we use a transgenic fish model, the λ transgenic medaka, to evaluate the potential mutagenicity of PFOS in vivo following a subchronic exposure of 30 days. The mutant frequency of cII target gene was 3.46 × 10(-5) in liver tissue from control fish, which increased by 1.4-fold to 4.86 × 10(-5) in fish exposed to 6.7 μg/L PFOS, 1.55-fold to 5.36 × 10(-5) in fish exposed to 27.6 μg/L PFOS, and 2.02-fold to 6.99 × 10(-5) in fish exposed to 87.6 μg/L PFOS. This dose-dependent increase of mutant frequency was also accompanied with mutational spectrum changes associated with PFOS exposure. In particular, PFOS-induced mutation was characterized by +1 frameshift mutations, which increased from 0% in control fish to 13.2% in fish exposed to 27.6 μg/L PFOS and 14.6% in fish exposed to 87.6 μg/L PFOS. Our findings provide the first evidence of PFOS's mutagenicity in an aquatic model system. Given the fact that most conventional mutagenic assays were negative for PFOS, we propose that PFOS-induced mutation in liver tissue of λ transgenic medaka may be mediated through compromised liver function.										-		C	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献ランク①	文献ランク②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1581	遺伝毒性	Eriksen, Kirsten Thorup; Raaschou-Nielsen, Ole; Sørensen, Mette; Roursgaard, Martin; Loft, Steffen; Møller, Peter	Genotoxic potential of the perfluorinated chemicals PFOA, PFOS, PFBS, PFNA and PFHxA in human HepG2 cells	2010	Mutat Res. 2010 Jul 19;700(1-2):39-43. doi: 10.1016/j.mrgentox.2010.04.024. Epub 2010 May 6.	Synthetically produced perfluorinated chemicals (PFCs) are widely used in industrial products because of their anti-wetting and surfactant properties. PFCs are suspected carcinogens and a possible mechanism of action is generation of oxidative stress. We have investigated the potential of five different PFCs to generate reactive oxygen species (ROS) and to induce oxidative DNA damage in HepG2 cells. Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) increased the intracellular ROS production by 1.52-fold (95% CI, 1.37-1.67) and 1.25-fold (95% CI, 1.10-1.40), respectively. However, the increase in ROS production was not concentration-dependent and the compounds did not generate DNA damage that could be detected by the alkaline comet assay as strand breakage and alkali-labile sites or formamidopyrimidine-DNA-glycosylase (FPG) sites. Perfluorobutane sulfonate (PFBS) and perfluorohexanoic acid (PFHxA) did not generate ROS or DNA damage. Only the exposure to perfluorononanoic acid (PFNA) caused a modest increase in DNA damage at a cytotoxic concentration level, which was detected as lactate dehydrogenase (LDH) release into the cell medium. This was not related to ROS generation. Collectively, these results indicate that PFCs induce only modest effects in terms of ROS production and DNA damage in a cell line representing the human liver.			●	●	●	●			●	-		B	-
1582	遺伝毒性	Liu, Changhui; Chang, Victor W C; Gin, Karina Y H; Nguyen, Viet Tung	Genotoxicity of perfluorinated chemicals (PFCs) to the green mussel (Perna viridis)	2014	Sci Total Environ. 2014 Jul 15;487:117-22. doi: 10.1016/j.scitotenv.2014.04.017. Epub 2014 Apr 27.	Concerns regarding perfluorinated chemicals (PFCs) have grown significantly in recent years. However, regulations and guidelines regarding the emission and treatment of PFCs are still missing in most parts of the world, mostly due to the lack of PFC toxicity data. In the current study, the genotoxic effects of four common PFCs, named perfluorooctanesulfonate (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA) and perfluorodecanoic acid (PFDA) were investigated on marine mussels. The effects of exposure time and concentration on the toxic behavior of the compounds were also examined. Genotoxicity of PFCs was assessed in biomarker assays, showing that exposure to the target compounds could damage the organism's genetic material to varying extents, including DNA strand breaks and fragmentation, chromosomal breaks and apoptosis. The adverse effects increased with both exposure concentration and time and were related with the organism burden of PFCs. The integrated biomarker response analysis demonstrated that PFOS exhibited a higher genotoxicity than the other tested compounds. The EC50 values and confidence intervals based on integrative genotoxicity were 33 (29-37), 594 (341-1036), 195 (144-265) and 78 (73-84) μg/L for PFOS, PFOA, PFNA and PFDA respectively, classifying PFOS as a highly genotoxic compound. Although primary DNA damage was shown to be recoverable after exposure ceased, permanent genetic damage caused by elevated PFC concentrations was not restored. This is the first ecotoxicity study of PFCs that focuses on the genotoxic effects of the compounds, clearly indicating the genotoxicity of the tested PFCs and demonstrating that functional groups have a major impact on the compounds' genotoxic behavior.			●							-		C	-
1583	遺伝毒性	Yahia, Doha; Haruka, Igarashi; Kagashi, Yae; Tsuda, Shuji	8-Hydroxy-2'-deoxyguanosine as a biomarker of oxidative DNA damage induced by perfluorinated compounds in TK6 cells	2016	Environ Toxicol. 2016 Feb;31(2):192-200. doi: 10.1002/tox.22034. Epub 2014 Aug 12.	8-Hydroxy-2'-deoxyguanosine (8-OHdG) is the most common biomarker of oxidative DNA damage, it is formed by chemical carcinogens and can be measured in any species. Perfluorooctanoic acid (PFOA) and perfluorononanoic acid (PFNA) are suspected genotoxic carcinogens through induction of reactive oxygen species that are responsible for oxidative DNA damage. This study was conducted to investigate the in vitro genotoxicity of PFOA and PFNA in human lymphoblastoid (TK6) cell line. TK6 cells were exposed to PFOA at 0, 125, 250, and 500 ppm and PFNA at 125 and 250 ppm for 2 h. Single cell gel electrophoresis (comet assay) was used to measure DNA damage; at least 50 cells per sample were analyzed using comet Assay Software Project (CASP). 8-OHdG was measured in DNA of exposed cells using high-performance liquid chromatography (HPLC)-mass spectrometry (MS)/MS. Results showed that both PFOA and PFNA induced DNA damage indicated by increased tail length (DNA migration). The level of 8-OHdG was increased in a dose-dependent manner in both PFOA and PFNA exposure. We concluded that PFOA and PFNA induced DNA damage and the biomarker of oxidative DNA damage (8-OHdG) could be measured by HPLC-MS/MS. In addition, PFNA produced high level of 8-OHdG at concentrations lower than PFOA, this may indicate that PFNA is more potent genotoxicant for TK6 cells than PFOA.			●						●	-		B	-
1584	遺伝毒性	Butenhoff, John L; Kennedy, Gerald L; Jung, Reinhard; Chang, Shu-Ching	Evaluation of perfluorooctanoate for potential genotoxicity	2014	Toxicol Rep. 2014 May 27;1:252-270. doi: 10.1016/j.toxrep.2014.05.012. eCollection 2014.	Perfluorooctanoate (PFOA) is a fully fluorinated eight-carbon fatty acid analog with exceptional stability toward degradation that has been used as an industrial surfactant and has been detected in environmental and biological matrices. Exposures to PFOA in the workplace and in the environment have continuously stimulated investigations into its potential human health hazards. In this article, the results of fifteen unpublished genotoxicity assays conducted with perfluorooctanoate (as either the linear or linear/branched ammonium salt (APFO) or the linear/branched sodium salt) are reported and include: seven mutation assays (three in vitro reverse mutation assays with histidine auxotrophic strains of Salmonella typhimurium, two in vitro reverse mutation assays with the tryptophan auxotrophic Escherichia coli WP2uvr strain, one in vitro mitotic recombination (gene conversion) assay with Saccharomyces cerevisiae D4, and an in vitro Chinese hamster ovary (CHO) HGPRT forward mutation assay); seven studies to assess potential for chromosomal damage (three in vitro CHO chromosomal aberration studies, an in vitro human whole blood lymphocyte chromosomal aberration study, and three in vivo mouse micronucleus assays); and an in vitro C3H 10T1/2 cell transformation assay. Although PFOA has not been demonstrated to be metabolized, all in vitro assays were conducted both in the presence and in the absence of a mammalian hepatic microsomal activation system. These assays were originally described in twelve contract laboratory reports which have been available via the United States Environmental Protection Agency public docket (Administrative Record 226) for over a decade; however, the details of these assays have not been published previously in the open scientific literature. With the exception of limited positive findings at high and cytotoxic concentrations in some assay trials which reflected the likely consequence of cytotoxic disruption of normal cellular processes and not a specific genotoxic effect, the results of the studies presented in this paper and other published results clearly demonstrate the absence of direct mutagenic or genotoxic risk associated with PFOA. This finding is consistent with the physical/chemical characteristics of PFOA and is supported by other published genotoxicity studies.				●						-	1	A	-
1585	遺伝毒性	Çelik, Ayla; Eke, Dilek; Ekinci, Seda Yaprak; Yıldırım, Seda	The protective role of curcumin on perfluorooctane sulfonate-induced genotoxicity: Single cell gel electrophoresis and micronucleus test	2013	Food Chem Toxicol. 2013 Mar;53:249-55. doi: 10.1016/j.fct.2012.11.054. Epub 2012 Dec 12.	Perfluorooctane sulfonate (PFOS) is a man-made fluorosurfactant and global pollutant. PFOS a persistent and bioaccumulative compound, is widely distributed in humans and wildlife. Therefore, it was added to Annex B of the Stockholm Convention on Persistent Organic Pollutants in May 2009. Curcumin is a natural polyphenolic compound abundant in the rhizome of the perennial herb turmeric. It is commonly used as a dietary spice and coloring agent in cooking and anecdotally as an herb in traditional Asian medicine. In this study, male rats were treated with three different PFOS doses (0.6, 1.25 and 2.5 mg/kg) and one dose of curcumin, from Curcuma longa (80 mg/kg) and combined three doses of PFOS with 80 mg/kg dose of curcumin by gavage for 30 days at 48 h intervals. Here, we evaluated the DNA damage via single cell gel electrophoresis or comet assay and micronucleus test in bone marrow in vivo. PFOS induced micronucleus frequency and decreased the ratio of polychromatic erythrocyte to normochromatic erythrocyte in bone marrow. Using the alkaline comet assay, we showed that all doses of the PFOS strongly induced DNA damage in rat bone marrow and curcumin prevented the formation of DNA damage induced by PFOS.				●					●	-	1	A	-
1586	遺伝毒性	Eke, Dilek; Çelik, Ayla	Curcumin prevents perfluorooctane sulfonate-induced genotoxicity and oxidative DNA damage in rat peripheral blood	2016	Drug Chem Toxicol. 2016;39(1):97-103. doi: 10.3109/01480545.2015.1041601. Epub 2015 May 7.	Perfluorooctane sulfonate (PFOS) is a man-made fluorosurfactant and global pollutant. PFOS a persistent and bioaccumulative compound, and it is widely distributed in humans and wildlife. Therefore, it was added to Annex B of the Stockholm Convention on Persistent Organic Pollutants in May 2009. Curcumin is a natural polyphenolic compound abundant in the rhizome of the perennial herb turmeric. It is commonly used as a dietary spice and coloring agent in cooking and anecdotally as an herb in traditional Asian medicine. In this study, male rats were treated with three different PFOS doses (0.6, 1.25, and 2.5 mg/kg) and one dose of curcumin, from Curcuma longa (80 mg/kg), and combined three doses of PFOS with 80 mg/kg dose of curcumin by gavage for 30 d at 48 h intervals. Here, we investigated the DNA damage via single-cell gel electrophoresis/comet assay and micronucleus test in rat peripheral blood in vivo. It is found that all doses of PFOS increased micronucleus frequency (p < 0.05) and strongly induced DNA damage in peripheral blood in two different parameters; the damaged cell percent and genetically damage index, and curcumin prevented the formation of DNA damage induced by PFOS. Results showed that curcumin inhibited DNA damage including GDI at certain levels at statistical manner, 30.07%, 54.41%, and 36.99% for 0.6 mg/kg, 1.25 mg/kg, and 2.5 mg/kg.				●					●	-	1	A	-
1587	遺伝毒性	Fernández Freire, P; Pérez Martin, J M; Herrero, O; Peropadre, A; de la Peña, E; Hazen, M J	In vitro assessment of the cytotoxic and mutagenic potential of perfluorooctanoic acid	2008	Toxicol In Vitro. 2008 Aug;22(5):1228-33. doi: 10.1016/j.tiv.2008.04.004. Epub 2008 Apr 15.	Perfluorooctanoic acid (PFOA) is a perfluorinated compound ubiquitously detected in the environment, including wildlife and humans. Despite the available information, research on the cytotoxicity of PFOA in non-tumoral mammalian cells is relatively limited. In this work, two in vitro toxicity systems were employed to provide further insight into the cytotoxic and mutagenic potential of PFOA. The cytotoxicity of the chemical towards Vero cells was assessed using biochemical and morphological parameters, while mutagenicity was evaluated according to Ames test. High doses of PFOA cause oxidative stress in Vero cells, that was closely linked to cell cycle arrest at the G1 phase and induction of apoptosis. Our results corroborate previous findings in human tumoral cells and suggest that the mode of action of this perfluorinated compound is not a peculiarity among mammalian cell types. On the other hand, the compound was not mutagenic in the Ames test, using four strains of Salmonella typhimurium in the presence or absence of rat S9 metabolic activation system.				●		●			●	-	1	A	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用									備考	情報抽出対象	文献ランク①	文献ランク②
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1588	遺伝毒性	Florentin, Arnaud; Deblonde, Tiphanie; Diguio, Nathalie; Hautemaniere, Alexis; Hartemann, Philippe	Impacts of two perfluorinated compounds (PFOS and PFOA) on human hepatoma cells: Cytotoxicity but no genotoxicity?	2011	Int J Hyg Environ Health. 2011 Nov;214(6):493-9. doi: 10.1016/j.ijheh.2011.05.010. Epub 2011 Jun 14.	Perfluorinated compounds (PFCs) and particularly two of them, perfluorooctanoate (PFOA) and perfluorooctanesulfonate (PFOS), have been widely produced and used since 1950. They both persist in the environment and accumulate in wildlife and humans. The toxicity of PFOS and PFOA has been studied extensively in rodents with several adverse effects mainly a hepatocarcinogenic potential. Carcinogenic effects are not highlighted in humans' studies. In this study, we investigated the cytotoxic and genotoxic effects of PFOA and PFOS using human HepG2 cells after 1 or 24h of exposure. The cytotoxic and genotoxic potential was evaluated by MTT assay, single cell gel electrophoresis (SCGE) assay and micronucleus assay respectively. We measured the intracellular generation of reactive oxygen species (ROS) using dichlorofluorescein diacetate to identify a potential mechanism of toxicity. We observed a cytotoxic effect of PFOA and PFOS after 24h of exposure starting from a concentration of 200 μM (MTT: -14.6%) and 300 μM (MTT: -51.2%) respectively. We did not observe an increase of DNA damage with the comet assay or micronucleus with the micronucleus assay after exposure to the two PFCs. After 24h of exposure, both PFOA and PFOS highlight a decrease of ROS generation (-5.9% to -23%). We did not find an effect after an hour of exposure. Our findings show that PFOA and PFOS exert a cytotoxic effect on the human cells line HepG2 but nor PFOA or PFOS could induce an increase of DNA damage (DNA strand breaks and micronucleus) or reactive oxygen species at the range concentration tested. Our results do not support that oxidative stress and DNA damage are relevant for potential adverse effects of PFOA and PFOS. These results tend to support epidemiological studies that do not show evidence of carcinogenicity.				●	●	●			●	-		B	-
1589	遺伝毒性	Jacquet, N; Maire, M A; Landkocz, Y; Vasseur, P	Carcinogenic potency of perfluorooctane sulfonate (PFOS) on Syrian hamster embryo (SHE) cells	2012	Arch Toxicol. 2012 Feb;86(2):305-14. doi: 10.1007/s00204-011-0752-8. Epub 2011 Nov 6.	Perfluorooctane sulfonate (PFOS) is the degradation product of many fluoroderivatives and a widespread environmental contaminant. Its persistence, its long half-life in humans and its toxicity explain high concerns on human health side effects in future. PFOS is suspected to be a non-genotoxic carcinogen. In the present work, we assessed carcinogenic potential of PFOS by studying morphological transformation in Syrian hamster embryo (SHE) cells; cell transformation of SHE cells is an in vitro assay recommended by the Organization for Economic Cooperation and Development to detect carcinogens, genotoxic or not. Genotoxicity of PFOS and expression of PPARs genes in SHE cells were also measured. PFOS was shown to induce cell transformation ($P < 0.05$) at non-cytotoxic concentrations (0.2 and 2 μg/mL) ($P \leq 0.01$). No genotoxic effect was recorded in the range of PFOS concentrations tested (2 × 10(-4) to 50 μg/mL) using the single-cell gel electrophoresis (comet) assay after 5 and 24 h of exposure. The expression of PPARs genes was measured by qPCR within the first 24 h and after 7 days of PFOS treatment. Results indicated an increased expression of ppar-β/δ isoform as early as 24 h. After 7 days, the increase of ppar-β/δ mRNA was significant at the concentrations inducing cell transformation (0.2 and 2 μg/mL), while overexpression of ppar-γ and ppar-α did not closely relate to effective concentrations. The results indicate that PFOS behave as a non-genotoxic carcinogen and impacted PPARs genes. Its cell transforming potential paralleled an increased expression of ppar-β/δ.				●	●				●	-		B	-
1590	遺伝毒性	Kawamoto, Kosuke; Oashi, Takahiro; Oami, Kazunori; Liu, Wei; Jin, Yihe; Saito, Norimitsu; Sato, Itaru; Tsuda, Shuji	Perfluorooctanoic acid (PFOA) but not perfluorooctane sulfonate (PFOS) showed DNA damage in comet assay on Paramecium caudatum	2010	J Toxicol Sci. 2010 Dec;35(6):835-41. doi: 10.2131/jts.35.835.	Persistent perfluorinated organic compounds such as perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) are distributed widely in the global environment including wildlife and human. In this study, we investigated the genotoxicity of PFOS and PFOA using the novel in vivo comet assay developed for Paramecium caudatum. For the comet assay, large nuclei squeezed out of the paramecia with 0.25 M sucrose containing 0.6% Triton X-100 were embedded in a layer of agarose gel placed over the slide glass. N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and 2-aminoanthracene (2-AA) were successfully used for positive controls. Productions of 8-hydroxydeoxyguanosine (8-OH-dG) and intracellular reactive oxygen species (ROS) were also measured in paramecia. PFOS did not cause DNA damage on any conditions examined. On the other hand, 12 and 24 hr exposure to PFOA (100 μM) increased DNA migration in electrophoresis condition at pH 13, but not at pH 12.1, suggesting that the DNA damage may be alkali labile site (such as apurinic/apyrimidinic (AP) site). Exposure of paramecia to 100 μM PFOA for 1, 3 and 24 hr and to 10 μM PFOA for 24 hr significantly increased intracellular ROS. Under the same condition, however, 8-OH-dG level was not affected by PFOA. The PFOA-induced DNA damage was not abolished by the application of 100 μM GSH which completely inhibited the increase of intracellular ROS. In conclusion, the PFOA-induced in vivo DNA damage was first shown in paramecia, and the DNA damage might not be directly attributable to increase in intracellular ROS.				●	●					-		C	-
1591	遺伝毒性	Oda, Yoshimitsu; Nakayama, Shoji; Harada, Kouji H; Koizumi, Akio	Negative results of umu genotoxicity test of fluorotelomer alcohols and perfluorinated alkyl acids	2007	Environ Health Prev Med. 2007 Sep;12(5):217-9. doi: 10.1265/ehpm.12.217.	OBJECTIVES: Recently, perfluorooctanoate (PFOA) has been ubiquitously detected in the environment as well as in human serum. Fluorotelomer alcohols (FTOHs), a precursor of PFOA, undergo biodegradation via several metabolic routes which leads to formation of various biodegradation products. The degradation of FTOHs produces an α,β-unsaturated aldehyde that seems possibly to be electrophilic and may react with cellular macromolecules including DNA. METHODS: We investigated the genotoxicity of three FTOHs (6∶2 FTOH, 8∶2 FTOH and 10∶2 FTOH), PFOA and perfluorooctane sulfonate (PFOS) using theumu test. RESULTS: The FTOHs, PFOA and PFOS showed no significant increases in β-galactosidase activity at 0-1000 μM in the absence of S9 mix. The results were unchanged by the metabolic activation with S9 mix. CONCLUSION: The genotoxicities of FTOHs, PFOA or PFOS are not detectable using the present method, suggesting that they are unlikely mutagens.				●	●	●			●	-		B	-
1592	遺伝毒性	Takagi, A; Sai, K; Umemura, T; Hasegawa, R; Kurokawa, Y	Short-term exposure to the peroxisome proliferators, perfluorooctanoic acid and perfluorodecanoic acid, causes significant increase of 8-hydroxydeoxyguanosine in liver DNA of rats	1991	Cancer Lett. 1991 Apr;57(1):55-60. doi: 10.1016/0304-3835(91)90063-n.	To elucidate the relationship between peroxisome proliferation by perfluorinated compounds and oxidative DNA damage, perfluorooctanoic acid (PFOA), perfluorodecanoic acid (PFDA), perfluorobutyric acid (PFBA) and perfluorooctane (PFO) were administered to 6-week-old F-344 male rats. After a single intraperitoneal (i.p.) injection of PFOA, PFBA or PFO in corn oil at a dose of 100 mg/kg, significant increases of liver weight and 8-hydroxydeoxyguanosine (8-OH-dG) levels in liver DNA were observed in PFOA-treated rats. Oral administration of powdered diet containing 0.02% PFOA or 0.01% PFDA for 2 weeks resulted in significant increases of liver weight and 8-OH-dG levels in liver DNA in rats given both chemicals. On the other hand, no increase in 8-OH-dG levels in kidney DNA was found in either of the studies. Our results demonstrate that, as with other peroxisome proliferators (phthalic ester plasticizers and hypolipidemic drugs), PFOA and PFDA induced peroxisome proliferation also leads to organ specific oxidative DNA damage.				●						-		B	-
1593	遺伝毒性	Yao, Xiaofeng; Zhong, Laifu	Genotoxic risk and oxidative DNA damage in HepG2 cells exposed to perfluorooctanoic acid	2005	Mutat Res. 2005 Nov 10;587(1-2):38-44. doi: 10.1016/j.mrgentox.2005.07.010. Epub 2005 Oct 10.	Perfluorooctanoic acid (C8HF15O2, PFOA) is widely used in various industrial fields for decades and it is environmentally bioaccumulative. PFOA is known as a potent hepatocarcinogen in rodents. But it is not yet clear whether it is also carcinogenic in humans, and the genotoxic effects of PFOA on human cells have not yet been examined. In this study, the genotoxic potential of PFOA was investigated in human hepatoma HepG2 cells in culture using single cell gel electrophoresis (SCGE) assay and micronucleus (MN) assay. In order to clarify the underlying mechanism(s) we measured the intracellular generation of reactive oxygen species (ROS) using dichlorofluorescein diacetate as a fluorochrome. The level of oxidative DNA damage was evaluated by immunocytochemical analysis of 8-hydroxydeoxyguanosine (8-OHdG) in PFOA-treated HepG2 cells. PFOA at 50-400 microM caused DNA strand breaks and at 100-400 microM MN in HepG2 cells both in a dose-dependent manner. Significantly increased levels of ROS and 8-OHdG were observed in these cells. We conclude that PFOA exerts genotoxic effects on HepG2 cells, probably through oxidative DNA damage induced by intracellular ROS.				●					●	-		B	-
1594	遺伝毒性	Zhao, Guoping; Wang, Jun; Wang, Xiaofei; Chen, Shaopeng; Zhao, Ye; Gu, Feng; Xu, An; Wu, Lijun	Mutagenicity of PFOA in mammalian cells: Role of mitochondria-dependent reactive oxygen species	2011	Environ Sci Technol. 2011 Feb 15;45(4):1638-44. doi: 10.1021/es1026129. Epub 2010 Dec 31.	Mutagenicity is often a prerequisite to the development of malignancy. Evidences have shown that exposure to perfluorooctanoic acid (PFOA) results in various cancer inductions. However, whether any mutagenic base exists is still puzzling. In the present study, we exposed exponentially growing AL cells to PFOA and assayed the cells for survival, mutation induction, and caspase-3/7, -9 activities. Mitochondrial-DNA deficient human-hamster hybrid (ρ(0) AL) cells and reactive oxygen species (ROS) inhibitor were used to elucidate the possible mechanism. Our results showed that treatment of AL cells with PFOA for 16 days induced significant mutagenic effects together with the increment of ROS, superoxide anions ($O2(.-)$), and nitrogen oxide (NO) levels, while treatment of ρ(0) AL cells did not have much change. Concurrent treatment of AL cells with ROS inhibitor significantly decreased the mutagenic potential of PFOA. In addition, caspase activities in AL cells were increased by PFOA exposure and suppressed by ROS/RNS (reactive oxygen/nitrogen species) inhibitors. Our results suggest that exposure to PFOA lead to mutagenicity induction in AL cells, and mitochondria-dependent ROS plays an important role in this process. This provides a direct base for PFOA mediated cancer induction.				●		●			●	-		B	-
1595	遺伝毒性	Health Canada	Perfluorooctane Sulfonate (PFOS) Its Salts and Its Precursors that Contain the $C8F17SO2$ or $C8F17SO3$ Moiety	2006	State of the science report for a screening health assessment, https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/ewh-semt/alt_formats/hecs-sesc/pdf/contaminants/existsub/pfos-spfo/perfluorooctane_sulfonate-eng.pdf	No abstract available					●					Health Canada ガイダンス		D	-
1596	遺伝毒性	Environment Canada and Health Canada	Screening assessment report perfluorooctanoic acid, its salts, and its precursors	2012	Available at https://ec.gc.ca/ese-ees/370AB133-3972-454F-A03A-F18890B58277/PFOA_EN.pdf	No abstract available						●				Environment Canada評価書		D	-
1597	遺伝毒性	Lindeman, Birgitte; Maass, Christine; Duale, Nur; Gü tzkow, Kristine B; Brunborg, Gunnar; Andreassen, Ashild	Effects of per- and polyfluorinated compounds on adult rat testicular cells following in vitro exposure	2012	Reprod Toxicol. 2012 Jul;33(4):531-537. doi: 10.1016/j.reprotox.2011.04.001. Epub 2011 Apr 17.	Testicular toxicity is observed following exposure of rats to per- and polyfluorinated compounds (PFCs). Such compounds were also shown to induce oxidative stress and changes in ABC efflux transporters e.g. P-gp, implying two mechanisms which may contribute to testicular toxicity. We studied the toxicity of four PFCs (PFOA, PFNA, 8:2 FTOH and 6:2 FTOH) on primary rat testicular cells. DNA damage was studied by the comet assay including Fpg enzyme treatment to detect oxidative lesions. The levels of the ABC efflux transporters Bcrp1, Oat2 and P-gp were studied by real-time RT-PCR or flow cytometry. A PFNA associated increase in DNA SSBs was attributed to a subpopulation of moderately damaged cells possibly associated with cytotoxicity. No significant increase in oxidative DNA damage was measured for any of the PFCs. Expression levels of ABC efflux transporters suggest that PFCs may increase expression levels of the P-gp protein and the Oat2 gene.						●			●	-		B	-
1598	遺伝毒性	UK HPA	HPA Compendium of chemical hazards PFOS + PFOA	2009	PHE publications gateway number: 2014790 (HPA has closed and became part of PHE in 2013)	No abstract available						●				詳細不明		D	-

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用 EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022	備考	情報抽出対象	文献ランク①	文献ランク②
1599	遺伝毒性	Environment Canada and Health Canada	Proposed risk management approach for perfluorooctanoic acid (PFOA), its salts, and its precursors and long-chain (C9-C20) perfluorocarboxylic acids (PFCAs), their salts, and their precursors	2012	Available at https://www.ec.gc.ca/ese-ees/451C95ED-6236-430C-BE5A-22F91B36773F/PFOA%20%26%20PFCAs_RMA_EN.pdf	No abstract available									●	Environment Canada評価書		D	-
1600	グルーピング	Cousins, I. T.; Dewitt, J. C.; Glüge, J.; Goldenman, G.; Herzke, D.; Lohmann, R.; Ng, C. A.; Scheringer, M.; Wang, Z.	The high persistence of PFAS is sufficient for their management as a chemical class	2020	Environ Sci Process Impacts;22(12):2307-2312. doi: 10.1039/D0EM00355G	Per- and polyfluoroalkyl substances (PFAS) are a class of synthetic organic substances with diverse structures, properties, uses, bioaccumulation potentials and toxicities. Despite this high diversity, all PFAS are alike in that they contain perfluoroalkyl moieties that are extremely resistant to environmental and metabolic degradation. The vast majority of PFAS are therefore either non-degradable or transform ultimately into stable terminal transformation products (which are still PFAS). Under the European chemicals regulation this classifies PFAS as very persistent substances (vP). We argue that this high persistence is sufficient concern for their management as a chemical class, and for all "non-essential" uses of PFAS to be phased out. The continual release of highly persistent PFAS will result in increasing concentrations and increasing probabilities of the occurrence of known and unknown effects. Once adverse effects are identified, the exposure and associated effects will not be easily reversible. Reversing PFAS contamination will be technically challenging, energy intensive, and costly for society, as is evident in the efforts to remove PFAS from contaminated land and drinking water sources.									●	-		D	-
1601	グルーピング	Cousins, I. T.; Dewitt, J. C.; Glüge, J.; Goldenman, G.; Herzke, D.; Lohmann, R.; Miller, M.; Ng, C. A.; Scheringer, M.; Vierke, L.; Wang, Z.	Strategies for grouping per- and polyfluoroalkyl substances (PFAS) to protect human and environmental health	2020	Environ Sci Process Impacts;22(7):1444-1460. doi: 10.1039/d0em00147c. Epub 2020 Jun 4.	Grouping strategies are needed for per- and polyfluoroalkyl substances (PFAS), in part, because it would be time and resource intensive to test and evaluate the more than 4700 PFAS on the global market on a chemical-by-chemical basis. In this paper we review various grouping strategies that could be used to inform actions on these chemicals and outline the motivations, advantages and disadvantages for each. Grouping strategies are subdivided into -1 those based on the intrinsic properties of the PFAS (e.g. persistence, bioaccumulation potential, toxicity, mobility, molecular size) and -2 those that inform risk assessment through estimation of cumulative exposure and/or effects. The most precautionary grouping approach of those reviewed within this article suggests phasing out PFAS based on their high persistence alone (the so-called "P-sufficient" approach). The least precautionary grouping approach reviewed advocates only grouping PFAS for risk assessment that have the same toxicological effects, modes and mechanisms of action, and elimination kinetics, which would need to be well documented across different PFAS. It is recognised that, given jurisdictional differences in chemical assessment philosophies and methodologies, no one strategy will be generally acceptable. The guiding question we apply to the reviewed grouping strategies is: grouping for what purpose? The motivation behind the grouping (e.g. determining use in products vs. setting guideline levels for contaminated environments) may lead to different grouping decisions. This assessment provides the necessary context for grouping strategies such that they can be adopted as they are, or built on further, to protect human and environmental health from potential PFAS-related effects.									●	-		B	-
1602	グルーピング	Kwiatkowski, Carol F; Andrews, David Q; Birnbaum, Linda S; Bruton, Thomas A; DeWitt, Jamie C; Knappe, Detlef R U; Maffini, Maricel V; Miller, Mark F; Pelch, Katherine E; Reade, Anna; Soehl, Anna; Trier, Xenia; Venier, Marta; Wagner, Charlotte C; Wang, Zhanyun; Blum, Arlene	Scientific Basis for Managing PFAS as a Chemical Class: Environmental Science & Technology Letters 7(8):532-543	2020	Environ Sci Technol Lett. 2020 Aug 11;7(8):532-543. doi: 10.1021/acs.estlett.0c00255. Epub 2020 Jun 30.	This commentary presents a scientific basis for managing as one chemical class the thousands of chemicals known as PFAS (per- and polyfluoroalkyl substances). The class includes perfluoroalkyl acids, perfluoroalkylether acids, and their precursors; fluoropolymers and perfluoropolyethers; and other PFAS. The basis for the class approach is presented in relation to their physicochemical, environmental, and toxicological properties. Specifically, the high persistence, accumulation potential, and/or hazards (known and potential) of PFAS studied to date warrant treating all PFAS as a single class. Examples are provided of how some PFAS are being regulated and how some businesses are avoiding all PFAS in their products and purchasing decisions. We conclude with options for how governments and industry can apply the class-based approach, emphasizing the importance of eliminating non-essential uses of PFAS, and further developing safer alternatives and methods to remove existing PFAS from the environment.									●	-		B	-
1603	リスク評価	Portier, K; Tolson, JK; Roberts, SM.	Body weight distributions for risk assessment	2007	Risk Anal. 27: 11-26. doi: 10.1111/j.1539-6924.2006.00856.x.	Precise age-specific average body weight estimates are necessary for deterministic risk assessments, and an accurate body weight distribution is equally important in probabilistic risk assessments. Age-specific body weight distributions for U.S. residents are estimated using NHANES (National Health and Nutrition Examination Survey) data collected in four surveys over the last 24 years. The weighted mean and standard deviation of natural log-transformed body weights are computed for single-year age groups and population age-specific weight patterns further described using piece-wise polynomial spline functions and nonparametric age-smoothed trend lines. These functions are used to compare distributional changes in age-specific body weight in the United States from the first NHANES survey in 1976-1980 to the most recent in 1999-2002. Analysis demonstrates that age- and sex-specific average body weight changes over this time period are not uniform. Use of these functions to compute body weight distributions for selected child-age categories is demonstrated.	●	●								-		C	C
1604	リスク評価	Hill, AB.	The environment and disease: Association or causation?	1965	Proc R Soc Med. 58: 295-300. doi: 10.1177/0141076814562718	No abstract available		●								-		D	C
1605	リスク評価	U.S. EPA	Methodology for deriving ambient water quality criteria for the protection of human health (2000)	2000	Available at https://www.epa.gov/sites/default/files/2018-10/documents/methodology-wqc-protection-hh-2000.pdf	This document provides technical support concerning cancer and noncancer risk assessment methods used in the Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (2000) (USEPA, 2000a; hereafter the 2000 Human Health Methodology). Ambient water quality criteria (AWQC) developed under Section 304(a) of the Clean Water Act (hereafter the CWA or the Act) are based solely on data and scientific judgments on the relationship between pollutant concentrations and environmental and human health effects. The 304(a) criteria do not reflect consideration of economic impacts or the technological feasibility of meeting the chemical concentrations in ambient water. As discussed below, 304(a) criteria are used by States and authorized Tribes to establish water quality standards, and ultimately provide a basis for controlling discharges or releases of pollutants.		●								-		C	C
1606	非発がんリスク	Peter Bannasch	Comments on R. Karbe and R. L. Kerlin (2002). Cystic degeneration/spongiosis hepatis (Toxicol Pathol 30 (2), 216-227)	2003	Toxicol Pathol.;31(5):566-70. doi: 10.1080/01926230390224700.	Karbe and Kerlin have questioned the classification of spongiosis hepatis as a preneoplastic lesion or even a benign neoplasm, designated as spongiotic pericytoma, and have proposed to use the term cystic degeneration for this lesion in rats and fish. However, the reclassification of spongiosis as cystic degeneration is unwarranted for several reasons. In the rat, spongiosis hepatis represents a specific pathomorphologic entity, originating from the perisinusoidal (Ito) cells; it may occur spontaneously in aged animals but its number and size increases significantly after exposure to various (hepato)carcinogens. Comparative morphological, immunohistochemical, and autoradiographic studies in rats exposed to N-nitrosomorpholine revealed that spongiosis hepatis is an integral part of larger proliferative Ito-cell aggregates showing an autonomous, progressive growth. The classification of spongiosis hepatis as a benign neoplasm is based on these findings that endorse and extend previous considerations on the preneoplastic or neoplastic nature of this lesion. Irrespective of the classification of spongiosis hepatis as a benign neoplastic or a preneoplastic lesion, there is compelling evidence for its reliability as a sensitive marker for (hepato)carcinogenic effects in rats and fish. The data collected by Karbe and Kerlin support rather than contradict the reliability of spongiosis hepatis as an effect marker for carcinogens.					●					-		C	C
1607	非発がんリスク	Bannasch, P. and Zerban, H.	Spongiosis hepatis and spongiotic pericytoma, rat	1997	Monographs on Pathology of Laboratory Animals. Springer-Verlag, Berlin. In book: Digestive System (pp.104-113) doi: 10.1007/978-3-662-25996-2_11	As a rule, the lesions of spongiosis are not visible with the naked eye. However, advanced lesions of this type may look like cysts at the macroscopic level.					●					-		D	C
1608	非発がんリスク	Delahunty, Caroline; Falconer, Shona; Hume, Robert; Jackson, Lesley; Midgley, Paula; Mirfield, Marie; Ogston, Simon; Perra, Oliver; Simpson, Judith; Watson, Jennifer; Willatts, Peter; Williams, Fiona	Levels of neonatal thyroid hormone in preterm infants and neurodevelopmental outcome at 5 1/2 years: millennium cohort study	2010	J Clin Endocrinol Metab. 2010 Nov;95(11):4898-908. doi: 10.1210/jc.2010-0743. Epub 2010 Aug 18.	CONTEXT: Transient hypothyroxinemia is the commonest thyroid dysfunction of premature infants, and recent studies have found adverse associations with neurodevelopment. The validity of these associations is unclear because the studies adjusted for a differing range of factors likely to influence neurodevelopment. OBJECTIVE: The aim was to describe the association of transient hypothyroxinemia with neurodevelopment at 5.5 yr corrected age. DESIGN: We conducted a follow-up study of a cohort of infants born in Scotland from 1999 to 2001 ≤34 wk gestation. MAIN OUTCOME MEASURES: We measured scores on the McCarthy scale adjusted for 26 influences of neurodevelopment including parental intellect, home environment, breast or formula fed, growth retardation, and use of postnatal drugs. RESULTS: A total of 442 infants ≤34 wk gestation who had serum T(4) measurements on postnatal d 7, 14, or 28 and 100 term infants who had serum T(4) measured in cord blood were followed up at 5.5 yr. Infants with hypothyroxinemia (T(4) level ≤ 10th percentile on d 7, 14, or 28 corrected for gestational age) scored significantly lower than euthyroid infants (T(4) level greater than the 10th percentile and less than the 90th percentile on all days) on all McCarthy scales, except the quantitative. After adjustment for confounders of neurodevelopment, hypothyroxinemic infants scored significantly lower than euthyroid infants on the general cognitive and verbal scales. CONCLUSIONS: Our findings do not support the view that the hypothyroxinemic state, in the context of this analysis, is harmless in preterm infants. Many factors contribute both to the etiology of hypothyroxinemia and neurodevelopment; strategies for correction of hypothyroxinemia should acknowledge its complex etiology and not rely solely on one approach.					●					-		C	C

No.	分野（参考）	著者	タイトル	発行年	書誌情報	要旨（原文）	評価書引用								備考	情報抽出対象	文献クラン①A	文献クラン②C
							EPA_PFOS_2021	EPA_PFOA_2021	EFSA_2020	ATSDR_2021	Health Canada_PFOS_2018	Health Canada_PFOA_2018	FSANZ_2017	FSANZ_2021 (Immunomodulation)	WHO_2022				
1609	非発がんリスク	Gilbert, Mary E; Rovet, Joanne; Chen, Zupei; Koibuchi, Noriyuki	Developmental thyroid hormone disruption: prevalence, environmental contaminants and neurodevelopmental consequences	2012	Neurotoxicology. 2012 Aug;33(4):842-52. doi: 10.1016/j.neuro.2011.11.005. Epub 2011 Nov 25.	Thyroid hormones (TH) are critical for growth and development and particularly brain development. There are numerous environmental agents that lead to marginal reductions of circulating TH. Although it is clear that severe developmental hypothyroidism is profoundly detrimental to neurodevelopment, there is less information regarding the consequences of modest degrees of thyroid. The impact of low level TH disruptions induced by environmental contaminants has not been defined. This paper is a synopsis from four invited speakers who presented at the 13th International Neurotoxicology Association meeting held in Xi'an, China during the summer of 2011. An overview of the role of TH in brain development and a review of human and animal data on the neurological sequelae of disruption of the thyroid axis in the pre- and early post-natal periods were presented by Mary Gilbert and Joanne Rovet. Iodine deficiency, a common cause of TH insufficiency and mental retardation in many countries, including China, was addressed by Zupei Chen. In this presentation the current incidence of iodine deficiency and neurological outcome in China and the efficacy of recently implemented iodinization programs to eliminate this cause of mental retardation were reviewed. Joanne Rovet described the impact of TH disruption during pregnancy and under conditions of congenital hypothyroidism. Children born with normal thyroid function, but who experienced TH insufficiency in the womb, display subtle cognitive impairments and abnormalities in brain imaging. Despite early detection and treatment, deficiencies also exist in children born with thyroid disorders. Different patterns of cognitive effects result from prenatal versus postnatal TH insufficiency. Mary Gilbert reported on the effects of environmental contaminants with thyroid disrupting action on brain development in animals. Results of neurophysiological, behavioral, structural and molecular alterations that accompany modest perturbations of the thyroid axis were reviewed. Noriyuki Koibuchi described molecular targets of TH-mediated signalling accompanying exposure to persistent organic pollutants. Both polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) are prevalent environmental contaminants that disrupt TH signalling at the receptor level. This action by these chemical classes could contribute to the negative impact of these chemicals on brain function. In summary, epidemiological, preclinical and animal research has clearly identified the critical role of TH in brain development. Additional work is required to understand the impact of low level perturbations of the thyroid axis to evaluate the risk associated with environmental contaminants with thyroid action.					●						-		A	C
1610	用量反応性解析	Hu, Jiayue; Li, Juan; Wang, Jianshe; Zhang, Aiqian; Dai, Jiayin	Synergistic effects of perfluoroalkyl acids mixtures with J-shaped concentration-responses on viability of a human liver cell line	2014	Chemosphere. 2014 Feb;96:81-8. doi: 10.1016/j.chemosphere.2013.07.033. Epub 2013 Aug 12.	Some perfluoroalkyl acids (PFAAs) are highly persistent and bioaccumulative, resulting in their broad coexisting distribution in humans and the environment. Our aim was to investigate the individual and joint effects of PFAAs on cellular viability of a human liver cell line (HL-7702) using the MTT assay. Equipartition ray design and equivalent-effect concentration ratio (EECR) mixtures were used to investigate the binary and multiple effects of PFAAs, respectively. All tested PFAAs mixtures and the individuals (except perfluorododecanoic acid (PFDoDA) and perfluorotetradecanoic acid (PFTeDA)) showed obvious non-monotonic J-shaped concentration-response curves (CRC) on HL-7702. The inhibitory effect of individual PFAAs increased with the elongation of the carbon chain and was dominated by their molecular volume. The three binary mixtures (PFOA/S, PFHxA/S and PFBA/S) showed that synergistic effects occurred under effective inhibitory concentrations (IC) of IC0, IC10, and IC50 in mixtures, while for IC-20 the synergistic effect only occurred under higher PFSA proportion in mixtures. Furthermore, EECR mixtures of the nine individual PFAAs with J-shaped CRC also showed synergistic effects. However, mixtures of the eleven individual PFAAs including those with S-shaped CRC resulted in partial addition effects on HL-7702. Our results indicated that the individual stimulatory responses of HL-7702 to PFAA may produce adverse effects in mixtures at relevant dose levels.					●	●					-		C	C
1611	非発がんリスク	Koibuchi, N; Chin, W W	Thyroid hormone action and brain development	2000	Trends Endocrinol Metab. 2000 May-Jun;11(4):123-8. doi: 10.1016/s1043-2760(00)00238-1.	Thyroid hormone (TH) plays a crucial role in brain development. Developing rodent cerebellum might be an excellent model for studying the molecular mechanisms of TH action in the brain because perinatal hypothyroidism greatly affects its ontogeny. Although the TH-regulated genes that play crucial roles in cerebellar development have not yet been fully characterized, recent studies have provided novel insights into TH action in brain development.					●						-		C	C
1612	非発がんリスク	Morreale de Escobar, Gabriella; Obregon, María Jesús; Escobar del Rey, Francisco	Role of thyroid hormone during early brain development	2004	Eur J Endocrinol. 2004 Nov;151 Suppl 3:U25-37. doi: 10.1530/eje.0.151u025.	The present comments are restricted to the role of maternal thyroid hormone on early brain development, and are based mostly on information presently available for the human fetal brain. It emphasizes that maternal hypothyroxinemia - defined as thyroxine (T4) concentrations that are low for the stage of pregnancy - is potentially damaging for neurodevelopment of the fetus throughout pregnancy, but especially so before midgestation, as the mother is then the only source of T4 for the developing brain. Despite a highly efficient uterine-placental 'barrier' to their transfer, very small amounts of T4 and triiodothyronine (T3) of maternal origin are present in the fetal compartment by 4 weeks after conception, with T4 increasing steadily thereafter. A major proportion of T4 in fetal fluids is not protein-bound: the 'free' T4 (FT4) available to fetal tissues is determined by the maternal serum T4, and reaches concentrations known to be of biological significance in adults. Despite very low T3 and 'free' T3 (FT3) in fetal fluids, the T3 generated locally from T4 in the cerebral cortex reaches adult concentrations by midgestation, and is partly bound to its nuclear receptor. Experimental results in the rat strongly support the conclusion that thyroid hormone is already required for normal corticogenesis very early in pregnancy. The first trimester surge of maternal FT4 is proposed as a biologically relevant event controlled by the conceptus to ensure its developing cerebral cortex is provided with the necessary amounts of substrate for the local generation of adequate amounts of T3 for binding to its nuclear receptor. Women unable to increase their production of T4 early in pregnancy would constitute a population at risk for neurological disabilities in their children. As mild-moderate iodine deficiency is still the most widespread cause of maternal hypothyroxinemia in Western societies, the birth of many children with learning disabilities may already be preventable by advising women to take iodine supplements as soon as pregnancy starts, or earlier if possible.					●						-		C	C
1613	非発がんリスク	Pop, V J; Kuijpens, J L; van Baar, A L; Verkerk, G; van Son, M M; de Vijlder, J J; Vulsma, T; Wiersinga, W M; Drexhage, H A; Vader, H L	Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy	1999	Clin Endocrinol (Oxf). 1999 Feb;50(2):149-55. doi: 10.1046/j.1365-2265.1999.00639.x.	BACKGROUND: Maternal thyroid function during early pregnancy is an important determinant of early fetal brain development because the fetal thyroid is unable to produce any T4 before 12-14 weeks' gestation. Overt maternal hypothyroidism as seen in severe iodine-deficient areas is associated with severely impaired neurological development of the offspring. At present, it is not known whether low free T4 (fT4) levels during pregnancy in healthy women from iodine sufficient areas may affect fetal neurodevelopment. METHODS: Neurodevelopment was assessed at 10 months of age in a cohort of 220 healthy children, born after uncomplicated pregnancies and deliveries, using the Bayley Scales of Infant Development. Maternal TSH, fT4 and TPO antibody status were assessed at 12 and 32 weeks' gestation. Maternal gestational fT4 concentration was defined as an independent parameter for child development. RESULTS: Children of women with fT4 levels below the 5th (< 9.8 pmol/l, n = 11) and 10th (< 10.4 pmol/l, n = 22) percentiles at 12 weeks' gestation had significantly lower scores on the Bayley Psychomotor Developmental Index (PDI) scale at 10 months of age, compared to children of mothers with higher fT4 values (t test, mean difference: 14.1, 95% confidence interval (CI): 5.9-22 and 7.4, 95% CI: 1.1-13.9, respectively). At 32 weeks' gestation, no significant differences were found. In the group of women with the lowest 10th percentile fT4 concentrations at 12 weeks' gestation, a positive correlation was found between the mothers' fT4 concentration and children's PDI scores (linear regression, R: 0.46, P = 0.03). After correction for confounding variables, a fT4 concentration below the 10th percentile at 12 weeks' gestation was a significant risk factor for impaired psychomotor development (RR): 5.8, 95% CI: 1.3-12.6). CONCLUSIONS: Low maternal plasma fT4 concentrations during early pregnancy may be an important risk factor for impaired infant development.					●						-		C	C
1614	非発がんリスク	Schroeder, A.C. and Privalsky, M.L.	Thyroid hormones, T3 and T4, in the brain	2014	Front. Endocrin., 5(40), 1–6. doi: 10.3389/fendo.2014.00040. eCollection 2014	No abstract available					●				-		D	D
1615	非発がんリスク	Schroeder, A.C. and Privalsky, M.L.	Recognition of, and differentiation between, adverse and non-adverse effects in toxicology studies	2002	ECETOC(2002) European Centre for Ecotoxicology and Toxicology of Chemicals, Brussels, Belgium (Technical Report No. 85).	No abstract available						●			評価書		D	D