

【事務局より】

疫学の公表文献10報がリスク管理機関から提出されました。

「No.」～「備考」は、基本的にリスク管理機関から提出された資料のままの記載としています。ただし、誤記と考えられた記載については赤字で修正しています。

各文献の研究結果の分類（「評価に使用する可能性のある文献」/「評価に使用しない文献」）及び判断理由について御検討ください。

文献No.1～3の横断研究について、「評価に使用する可能性のある文献」と考えられる場合は、評価書の記載案（疫学）も併せて御確認ください。

文献No.4及び5の症例報告について、摂取したフィプロニルの量が報告されておらず、適切なばく露情報がないため、「評価に使用しない文献」に分類する案としました。

文献No.6及び7の症例報告について、摂取したフィプロニルの濃度及び量が報告されているため、「評価に使用する可能性のある文献」とし、評価書の記載案（疫学）を作成しています。

文献No.8～10について、海外評価書で参照されていますが、フィプロニルに関する情報がないため「評価に使用しない文献」に分類する案としました。

御検討ください。

【本間専門委員より】

特にコメントはありません。

1. 文献情報

通しNo.	No.	文献名	ジャーナル名等	公表年	著者名	著者の所属機関	書誌情報	原著/総説	海外評価書での引用の有無	ドシエでの引用の有無	備考	研究結果の分類	分類の判断理由	事象(疾病等)
1	5-1-28	Thyroid function tests in persons with occupational exposure to fipronil.	Thyroid, Vol. 21 (7), p. 701-706	2011	Herin et al.	National Institute of Health and Medical Research (INSERM) and The University Paul Sabatier, Toulouse, France	<a href="https://doi.org/10.1089/thy.2010.0449">https://doi.org/10.1089/thy.2010.0449</a>	Original paper	○ EPA JMPR (2021)	-	The study focuses on the assessment of a putative correlation between fipronil exposure and altered thyroid hormone homeostasis. The authors found a correlation between fipronil exposure and fipronil and fipronil sulfone concentration in the serum. The metabolite fipronil sulfone was found more often than fipronil since the latter has a short half-life in blood serum. Serum fipronil sulfone concentration was found to be <b>negatively</b> correlated with TSH levels in exposed workers. However, the authors were not able to show a correlation between fipronil exposure and an increased <b>incidence in thyroid</b> hormone abnormalities. <span style="border: 1px solid black; padding: 2px;">井上専門参考人修文</span>	評価に使用する可能性のある文献 or 評価に使用しない文献		1. 甲状腺機能等
2	5-1-43	Distribution of fipronil in humans, and adverse health outcomes of in utero fipronil sulfone exposure in newborns.	International Journal of Hygiene and Environmental Health, Vol. 222 (3), p. 534524 -532	2019	Kim et al.	Departments of Obstetrics and Gynecology, Inje University Ilsan Paik Hospital, Goyang-si, Republic of Korea.	<a href="https://doi.org/10.1016/j.ijheh.2019.01.009">https://doi.org/10.1016/j.ijheh.2019.01.009</a>	Original paper	○ EPA JMPR (2021)	-	The study focuses on putative correlations between fipronil exposure measured by the fipronil sulfone level and altered thyroid hormone homeostasis in newborn child. The authors found a statistically significant negative correlation between umbilical blood levels of fipronil sulfone and triiodothyronine (T3), free T3 and 5-min Apgar scores mainly in models adjusted for different demographic, physiological, behavioral, socioeconomic, and clinical data. No correlation between fipronil sulfuron and thyroxine (T4) or TSH levels was observed.	評価に使用する可能性のある文献 or 評価に使用しない文献		1. 甲状腺機能等
3	6-1-15	Fipronil and its metabolites in human seminal plasma from shijiazhuang, north china	Chemosphere (Feb 2022), Volume 289 (133238 ISSN: 130045-136535	2022	Xu et al.	Key Laboratory of Environment and Health (HUST), Ministry of Education & Ministry of Environmental Protection, And State Key Laboratory of Environmental Health (Incubation), School of Public Health, Tongji Medical College, Huazhong University of Science and Technology	<a href="https://www.sciencedirect.com/journal/chemosphere">https://www.sciencedirect.com/journal/chemosphere</a>	original paper	-	-		評価に使用する可能性のある文献 or 評価に使用しない文献		2. 精液への影響

【與語専門委員より】  
「評価に使用する可能性のある文献or評価に使用しない文献」となっているものについては、全て評価に使用する可能性があると判断しました。

【池原専門参考人より】  
通しNo.1~3について:評価に使用する可能性のある文献

【井上専門参考人より】  
通しNo.1~3について:評価に使用する可能性のある文献

4	5-1-8	Fipronil compound consumption presenting as status epilepticus.	Toxicology International 22(1):165-6.	2015	Bharathraj M.Y et al.	Vijayanagara Institute of Medical Sciences, India	<a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4721168/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4721168/</a>	Original paper	○ JMPR PartII-Toxicologies (2021)	-	A remedial case of a 25-year-old male with an alleged history of fipronil compound consumption.	評価に使用しない文献	・摂取したフィプロニル含有物の濃度及び量が報告されておらず、適切なばく露情報がない。	3. 症例報告
5	8-1-37	Acute illnesses associated with exposure to fipronil—surveillance data from 11 states in the United States, 2001–2007	Clinical Toxicology (2010), Vol. 48 (7), p. 737-744	2010	Soo-Jeong et al.	National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Cincinnati, USA	<a href="https://doi.org/10.3109/15563650.2010.507548">https://doi.org/10.3109/15563650.2010.507548</a>	Original paper	○ EPA (2020)	-	The study focuses on patients with acute toxicity symptoms after exposure to fipronil under different circumstances and with different products. The typical symptoms after exposure were neurological, ocular, gastrointestinal and/or respiratory symptoms. Overall, the majority of effects was classified to be of low severity. Furthermore, the authors report three different cases of exposure with different outcomes showing the variety in symptoms upon exposure to fipronil. Overall, the authors conclude, that fipronil poses a low risk of mild, temporary health effects upon non-occupational exposure. However, the two most severe cases were found in two workers leading to the conclusion, that an occupational repeated exposure might lead to more severe symptoms.	評価に使用しない文献	・摂取したフィプロニルの量が報告されておらず、適切なばく露情報がない。	3. 症例報告
6	8-1-52	A case of accidental ingestion of ant bait containing fipronil	Journal of Toxicology: Clinical Toxicology (2003), Vol. 41 (3), p. 245-248	2003	Fung et al.	Accident and Emergency Department, Tuen Mun Hospital, Hong Kong	<a href="https://doi.org/10.1081/CLT-120021106">https://doi.org/10.1081/CLT-120021106</a>	Original paper	○ JMPR (2021)	-	The accidentally ingested ant bait led to a mild subjective impairment of sensorium which resolved spontaneously approximately half an hour later. The patient was discharged from the medical ward after a short period of observation within which no clinical signs occurred. No clinical signs or effects on haematology, clinical chemistry, liver function or renal function were observed approximately 2 weeks later. The authors state, that fipronil ingestion most likely causes mild symptoms. However, they also discuss the fact, that higher purity products or significant doses might result in more severe effects.	評価に使用する可能性のある文献		3. 症例報告

通しNo.	No.	文献名	ジャーナル名等	公表年	著者名	著者の所属機関	書誌情報	原著/総説	海外評価書での引用の有無	トシエでの引用の有無	備考	研究結果の分類	分類の判断理由	事象(疾病等)
7	8-1-53	Acute human self-poisoning with the N-phenylpyrazole insecticide fipronil – a GABAA-gated chloride channel blocker.	Journal of Toxicology: Clinical Toxicology (2004), Vol. 42 (7), p. 955-963	2004	Mohamed et al.	South Asian Clinical Toxicology Research Collaboration, Department of Clinical Medicine, University of Colombo, Colombo, Sri Lanka	<a href="https://doi.org/10.1081/CLT-200041784">https://doi.org/10.1081/CLT-200041784</a>	Original paper	○ JMPR (2021)	–	The study describes 8 cases of self poisoning with a plant protection product containing fipronil. From these, 5 consumed fipronil together with alcohol and/or other pesticides. For the remaining 3 cases consuming most likely only fipronil containing products the symptoms showed a great variety between acute symptoms like vomiting, nausea and heart burn to unconsciousness and subsequent death of the patient. However, it was not clear if the patient dying ingested fipronil only. All surviving patients were asymptomatic within 12 h after ingestion. Pharmacokinetics assessment indicated a rapid absorption followed by a rapid disappearance from the blood during the first 15-20h. This was followed by a plateau level of the paternal fipronil and metabolism of fipronil sulfone.	評価に使用する可能性のある文献		3. 症例報告
8	8-1-13	Utility of the 5-minute Apgar Score as a Research Endpoint.	American journal of epidemiology 188(9), 1695-1704	2019	Marit L. Bovbjerg et al.	Oregon State University	<a href="https://doi.org/10.1093/aje/kwz132">https://doi.org/10.1093/aje/kwz132</a>	Original paper	○ EPA (2019)	–	The publication was considered not to be relevant, since it does not contain information on the active substance fipronil.	評価に使用しない文献	・EPAでは、文献No.5-1-43の評価に当たり、アプガースコアに係る文献として引用しているが、フィプロニルに関する情報は記載されていない。	該当せず
9	8-1-24	Anticonvulsants and thyroid function.	British Medical Journal (6127):1581-1583.	1978	Yeo PP et al.	Glasgow Royal Infirmary, UK	<a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1605396/pdf/brmedj00130-0019.pdf">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1605396/pdf/brmedj00130-0019.pdf</a>	Original paper	○ JMPR PartII-Toxicologies (2021)	–	The publication was considered not to be relevant, since it does not contain information on the active substance fipronil.	評価に使用しない文献	・JMPRでは、フィプロニルの甲状腺への影響に係るヒトへの外挿性を検討するに当たり、ヒトにおける甲状腺ホルモン代謝に係る文献の一つとして引用されているが、フィプロニルに関する情報は記載されていない。	該当せず
10	8-1-60	Farm worker exposure to terbufos [phosphorodithioic acid, S-(tert-butylthio) methylO,O-diethyl ester] during planting operations of corn	Archives of Environmental Contamination and Toxicology (1986), Vol. 15 (1), p. 113-119	1986	Devine et al.	Cyanamid Canada Inc., Agricultural Products Department, Ontario, Canada	<a href="https://doi.org/10.1007/BF01055256">https://doi.org/10.1007/BF01055256</a>	Original paper	○ EFSA (2004)	–	The publication was considered not to be relevant, since it does not contain information on the active substance fipronil.	評価に使用しない文献	・EFSAでは、作業者のばく露量推定に当たり引用しているが、フィプロニルに関する情報は記載されていない。	該当せず
11		Multiple pesticides in mothers hair samples and childrens measurements at birth: Results from the French national birth cohort (ELFE)	International Journal of Hygiene and Environmental Health (2020), 223(1), 22-33	2020	Beranger, Remi; Hardy, Emilie M.; Binter, Anne-Claire; Charles, Marie-Aline; Zaros, Cecile; Appenzeller, Brice M. R.; Chevrier, Cecile	Chu Rennes, Inserm, Ehesp, Irset (Institut De Recherche En Sante, Environnement Et Travail), UmrS 1085, Univ Rennes, Rennes, F-35000, Fr.	PMID: 31708466 DOI: 10.1016/j.ijheh.2019.10.010	原著	–	–		評価に使用する可能性のある文献		出生児低体重等

【事務局より】  
No.11は、フィプロニルの疫学以外に分類されていたNo.5-1-12(総説)の引用文献の一つで、フィプロニルを含む複数の農業に関する疫学文献です。イミダクロプリドで「評価に使用する可能性のある文献」と判断されており、追記しました。  
机上配布資料1も併せて御確認ください。

2. 研究結果詳細

通し No.	No.	著者名	研究デザイン							健康関連の事象の情報							備考（他の文献との関連等）	事象（疾病等）		
			国名（地域名、研究名）	試験設計	調査時期	対象者、年齢	アウトカムの定義	アウトカムの確認方法	ばく露指標の定義	ばく露の確認方法	試験全体のN数（症例/対照）	アウトカムのN数（症例）	分析カテゴリー	ばく露に係るN数（症例/対照）	相対リスク/オッズ比等	95%信頼区間			p値	交絡因子の考慮
1	5-1-28	Herin et al.	France	Biomonitoring survey	2008	Factory workers manufacturing fipronil containing veterinary drugs 34.1 (± 7.5) years	Thyroid-stimulating hormone (TSH) homeostasis and thyroid function test (total T4 (TT4) and free T4 (FT4))	Automated immunoassay system	Years of employment	Serum concentration of fipronil and its metabolite fipronil sulfone via mass spectrometry	159 (159/0)	33 workers with detectable serum fipronil concentration 155 workers with detectable serum fipronil sulfone concentration	Correlation coefficients between serum fipronil or fipronil sulfone concentration and serum FT4, TT4, and TSH concentrations	159/0	-	-	-	Levothyroxin treatment, oral contraceptives, pregnancies, treatment for hypothyroidism after thyroidectomy, Hashimoto's thyroiditis or idiopathic hypothyroidism.	The study focuses on workers in a single factory manufacturing fipronil containing veterinary drugs.	1. 甲状腺機能等
2	5-1-43	Kim et al. (2019)	Republic of Korea	Biomonitoring survey	2013 - 2015	Matching pregnant women-newborn infant pairs and biological fathers if available Women: 32.08 (± 3.23) years Men: 34.31 (± 4.43) years	Thyroid hormone homeostasis/ thyroid function, Apgar scores	Electrochemiluminescence immunoassay, questionnaire survey	Serum fipronil and fipronil sulfone levels	LC-MS/MS Analysis	59 women and newborn infant pairs, 51 matching fathers (169/0)	-	Regression models	169 (169/0) based on fipronil sulfone	Beta coefficient: T3: Crude: -0.066 Model I: -0.104 Model II: -0.105 Free T3: Model I: -0.021 Model II: -0.021 5-min Apgar score: Model I: -0.538 Model II: -0.477	T3: Crude: -0.130, -0.001 Model I: -0.177, -0.029 Model II: -0.190, -0.020 Free T3: Model I: -0.037, -0.004 Model II: -0.040, -0.002 5-min Apgar score: Model I: -1.061, -0.015 Model II: -0.902, -0.051	<0.05	Small sample size, lacking dietary data although fipronil intake was considered mainly to occur via dietary intake, lack of information on serum lipid levels. Causal association is questionable since it was a cross sectional study based on blood sample analysis and demographic, physiological, behavioral, socioeconomic and clinical data simultaneously collected.	Based on their findings, the authors conclude, that fipronil is rapidly metabolised to fipronil sulfone in human, since fipronil was found only in one person and that fipronil placentally transfers from the mother to the unborn child. Additionally, the authors were able to show, that fipronil exposure correlates with the maternal pre-pregnant body mass index (BMI). They showed, that an inverse association between infant serum fipronil sulfone levels and T3 and free T3 levels and 5-min Apgar score does exist. This leads them to the assumption, that there is evidence between fipronil exposure and developmental defects via effects on thyroid hormone homeostasis. No correlation for T4 and TSH levels was found. The Models "Crude", "Model I" and "Model II" shown in column Q refer to different adjustment factors. Only statistically significant alterations were included.	1. 甲状腺機能等
3	6-1-15	Xu et al.	China	Biomonitoring	2018.11~2019.01	Chinese (20~30 years old and above)	Adversed effect on Semen quality ((sperm count, sperm concentration, total motility, fast and slow progressive motility, non-progressive motility, and immobilized sperm)	Statistical analysis of association between 1) fipronil and its metabolites in seminal plasma and 2) semen quality	Concentration of fipronil, fipronil desulfinyl, fipronil sulfone, fipronil amide and fipronil sulfide in seminal plasma	LC/MS Analysis	200	-	Concentration analysis of fipronil and its metabolites in individual semen sample	semen plasma : 200	-	-	-	FPS' levels in seminal plasma were related to BMI, education level, smoking status, and sexual frequency.	In this study, human seminal plasma was analyzed for the occurrence of Fipronil and its transformation products. The cumulative concentration of Fipronil and its transformation products in the seminal plasma samples ranged from 0.003 to 0.180 ng/mL (median: 0.043 ng/mL). Fipronil sulfone was identified as the major transformation product, accounting for approx. 42.3-100.0% of all Fipronil analytes. No significant association between Fipronil and impaired semen quality parameters was found. the data of the following publications were referred (Table 4).	2. 精液への影響
4	5-1-8	Bharathraj M.Y et al.	インド	症例報告	2015	男性、25才	-	-	摂取歴	-	1/0	-	-	1/0	-	-	-	-	救急で搬送された25才男性の症例報告。	3. 症例報告
5	8-1-37	Soo-Jeong et al.	米国	症例研究	2001-2007	中毒患者	健康影響	データベースの記録	使用の有無及び状況	データベースの記載	-/0	-	SAS v 9.1	103/0	-	-	-	暴露の確実性、健康影響、	中毒の症例を特徴づけ、製品種類ごとに層別化。	3. 症例報告
6	8-1-52	Fung et al.	中国	症例報告	2003	女性、77才	-	-	摂取の有無	患者へのインタビュー	1/0	-	-	1/0	-	-	-	-	77才女性の症例報告及び動物実験での毒性との比較検討。	3. 症例報告
7	8-1-53	Mohamed et al.	スリランカ	症例報告	2002	中毒患者	-	-	摂取の有無	患者へのインタビュー、初見の医師の手紙、血中濃度分析	7/0	-	-	7/0	-	-	-	-	フィプロニル中毒における活性炭の単回及び複数回投与の臨床研究における症例報告。	3. 症例報告
8	8-1-13	Marit L. Bovbjerg et al.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Determine optimal cutpoints for Apgar scores.	該当せず
9	8-1-24	Yeo PP et al.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Serum total and free thyroid hormone concentrations were estimated in 42 patients with epilepsy taking anticonvulsants (phenytoin, phenobarbitone, and carbamazepine either singly or in combination).	該当せず
10	8-1-60	Devine et al.	Canada	Biomonitoring survey	1982	Corn farmers	Urinary alkyl phosphate levels; plasma and red blood cell cholinesterase values	Potentiometric method of Michel; Morgan et al. 1979; Franklin et al. 1981	Dermal and respiratory exposure	Air collection tubes and dermal patches	11 farmers applying terbufos + 5 farmers which did not apply terbufos	-	-	-	11/0	-	-	-	In this study 11 farmers were monitored for exposure to terbufos. The average estimated exposure was 72 µg/h for dermal and 11 µg/h for respiratory exposure. However, no absorption of terbufos was observed as the results of urinary alkyl phosphate analyses were negative. Plasma and red blood cell cholinesterase activities were unchanged, hence there were no adverse effects of exposure. However, fipronil was not part of this study.	該当せず
11		Beranger, Remi; Hardy, Emilie M.; Binter, Anne-Claire; Charles, Marie-Aline; Zaros, Cecile; Appenzeller, Brice M. R.; Chevrier, Cecile	France (ELFE cohort)	横断研究	2011	妊婦及び新生児	新生児: 体重, 身長, 頭囲	病院内の記録	尿中の濃度	ultraperformance liquid chromatography tandem-mass spectrometry (UPLC-MS/MS)	311	n/a	Multivariable linear regression (not categorical)	記載なし	フィプロニル: 男児の体重との間に正の関連 (濃度の対数の標準偏差の2倍増加当たりの調整済み回帰係数: 169 g)	フィプロニル: 24~314 g	-	母親の年齢、身長、体重、出産回数、喫煙及び飲酒	出生児低体重等	