EFSA's draft scientific opinion on bisphenol A (BPA)

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Food Safety Seminar on Bisphenol A
Tokyo, 19 June 2014

ビスフェノールA（BPA）に関する EFSAの科学的意見書案について

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Food Safety Seminar on Bisphenol A
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Disclaimer

The content of this presentation does not necessarily represent the position of the European Food Safety Authority

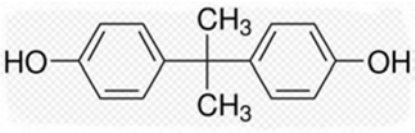
注意事項

本プレゼンテーションの内容は、必ずしもEFSAの立場を表明しているものとは限りません。

Bisphenol A (BPA): legislation in the EU

- BPA is authorised in the European Union as a **monomer** or other starting substance for the manufacture of plastic food contact materials with a specific migration limit of 0.6 mg/kg food.

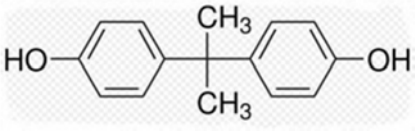
- BPA cannot be used to manufacture polycarbonate infant feeding bottles or as **additive** in plastic food contact materials and articles (Commission Regulation (EU) No 10/2011)



BPA: EUにおける法規

- BPAは、EUにおいては、特定移行限度を食品1kgあたり0.6 mgとするプラスチック製食品接触材料の製造の**単量体（monomer)**、もしくは、その他の出発物質として認可されている。

- BPAは、ポリカーボネート製の哺乳瓶の製造、もしくは、プラスチック製の食品接触材料の**添加剤**として用いることはできない。(Commission Regulation (EU) No 10/2011)



Overview of EFSA's work on BPA

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(1) HAZARD IDENTIFICATION

(2) HAZARD CHARACTERISATION

ADME, acute/sub/chronic toxicity, geno/repro/immuno-toxicity, mode of action, human data, dose-response for critical effect, point of departure (NOAEL, BMDL, etc), set of TDI

2006,2008,2010,2011,2013

(3) EXPOSURE ASSESSMENT

Occurrence data × Food consumption = EXPOSURE

Relevant food groups, adults and specific groups of the population, time trends

2006, 2013

(4) RISK CHARACTERISATION

2006, 2013

Relates exposure to a chemical in a given population with toxicological effects and concludes on the likelihood of adverse effects.

BPAに関するEFSAの取組みの概要

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(1) 危害要因の特定

(2) 危害要因の判定

吸収・分布・代謝・排泄、急性／亜急性／慢性毒性、遺伝／生殖／免疫毒性、作用機序（mode of action）, ヒトにおけるデータ、臨界影響に関する用量-反応、出発点 (NOAEL, BMDL, etc), TDIの設定

2006,2008,2010,2011,2013

(3) 暴露評価

検出データ × 食品の消費量 = 暴露量

関連食品群、成人及び特定の集団、時間的傾向

2006, 2013

(4) リスクの判定

2006, 2013

特定の集団における化学物質への暴露を毒性学的影響と関連付け、有害影響が示される可能性についての結論を出す。

Previous opinions by EFSA (2006, 2008, 2010, 2011)

2006: Full risk assessment

- TDI = 50 μg/kg b.w./day
- Dietary intake of infants and children: well below the TDI

2008: opinion on BPA Toxicokinetics

- BPA is safe at current exposure levels for fetuses, newborns & children

2010: Hazard characterisation of BPA

- TDI of 50 μg/kg b.w./day is reconfirmed (one minority opinion)
- Uncertainties for low dose effects on brain, immune system, and breast cancer in developing animals

2011: Panel Statement on the ANSES' report on BPA health effects

- TDI and uncertainties expressed by EFSA in 2010 are re-confirmed.
- The Panel needs to review more in depth the new literature

EFSAが過去に公表した意見書 (2006, 2008, 2010, 2011)

2006: 完全なリスク評価

- TDI = 50 μg/kg b.w./day
- 乳幼児及び小児の食事を介した摂取量: 上記TDIを十分に下回る

2008: BPAのトキシコキネティクスに関する意見

- BPAは、胎児、新生児及び小児については、現在の暴露レベルで安全である

2010: BPAの危害要因の判定

- TDI (50 μg/kg b.w./day)を再確認 (少数派の意見が1件)
- 成長中の動物における脳、免疫系及び乳がんの発生に対する低用量BPAの影響に関する不確実性

2011: BPAの健康影響に関するANSES(フランス食品環境労働衛生安全庁)の報告書についてのパネルの意見

- EFSAが2010年に公表したTDI及び不確実性を再確認
- パネルは、新たな文献をさらに深くレビューする必要を指摘

2012-2014: Self mandate of the CEF Panel on BPA

Mandate for a **Scientific Opinion on the risks to public health related to the presence of bisphenol A in foodstuffs**

1.To assess human exposure from **dietary** and **non-dietary** sources (including the supposedly vulnerable groups), and also account for biomonitoring data;

2.To evaluate the **toxicity for humans**, including the supposedly most vulnerable groups (e.g. pregnant women, infants and children, etc.);

3.To characterize the **health risks** for the general population and for supposedly vulnerable groups

Deadline: December 2014

2012-2014: CEFパネルによるBPAに関する自ら評価

食品におけるBPAの存在に関係する公衆衛生リスクについての科学的意見書のための達成目標

1. **食事由来**及び**食事由来でない**暴露源からのヒトの暴露を評価し（弱者と見なされる集団を含む）、バイオモニタリングデータを説明する

2. ヒトに対する毒性を評価する（もっとも弱者と見なされる集団（例：妊婦、乳幼児及び小児など）を含む

3. 一般集団及び脆弱と見なされるグループの**健康へのリスク**を判定する

締め切り: 2014年12月

Current risk assessment of BPA

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Two step approach

1. **Draft exposure assessment**:
   Endorsement by the CEF Panel: 4 July 2013
   Public consultation: 25 July - 15 September 2013

2. **Draft assessment of human health risks**:
   Endorsement of by the CEF Panel: 12 December 2013
   Public consultation: 17 Jan – 13 March 2014

現在のBPAに関するリスク評価

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二段階のアプローチ

1. **暴露評価の案**:
   CEFパネルによる結果とりまとめ: 2013年7月4日
   パブリックコメント: 2013年7月25日～9月15日

2. **ヒトの健康影響評価の案**:
   CEFパネルによる結果とりまとめ: 2013年12月12日
   パブリックコメント: 2014年1月17日～3月13日

Way forward after public consultations

Almost **500 comments** as a result of 2-phase public consultation!!

Next steps

Opinion finalization (by Dec 2014)

- Revisions prior to adoption by the CEF Panel

EFSA technical report (by Dec 2014)

- **Annex** listing all original comments in full, also disclosing the organisation's name
- **Overall summary of comments** by topic & **explanation of the actions taken with the rationale**

パブリックコメント後の予定

二段階のパブリックコメントの結果、約500件のコメント！

次のステップ

意見書の最終とりまとめ (2014年12月までに)

- CEFパネルによる採択の前に修正

EFSAの技術的報告書 (2014年12月までに)

- **別添** 全てのコメント(オリジナル)全体を掲載し、機関の名称も公開する
- **コメントの総合的な概要**(トピックごと)& **措置についての根拠を伴う説明**

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Draft assessments of bisphenol A (BPA) Exposure and Human Health Risks

European Food Safety Authority

BPAへの暴露及び ヒトの健康影響リスクに関する評価案

Outline

- Draft exposure assessment
  - Dietary exposure
  - Non-dietary exposure
- Draft assessment of human health risks
  - Hazard identification
    - Weight of evidence (WoE) approach to identify “likely” effects
  - Hazard characterisation for likely effects
    - BMD modelling
    - HED approach
  - Risk characterisation

概要

- 暴露評価案
  - 食事由来の暴露
  - 食事由来でない暴露
- ヒトの健康影響リスクの評価案
  - 危害要因の特定
    - 「起こる可能性のある」影響を特定するための、証拠の重み付け（Weight of evidence, WoE)を用いた方法
  - 起こる可能性のある影響についての危害要因の判定
    - ベンチマークドーズモデル
    - ヒト等価用量（HED）アプローチ
  - リスクの判定

Draft exposure assessment: General approach

- **Assessment** in the EU population of:
  - **Chronic** exposure to BPA via
  - **different sources** (diet, thermal paper, air, dust, toys, cosmetics)
  - **different routes of exposure** (dietary, oral non-dietary, dermal, inhalation)
  - in **different age classes** (supposedly most vulnerable groups: infants, children and women of childbearing age to address exposure of fetuses and in breastfed infants).

- For each source of exposure and in each age group **exposure scenarios** were developed to cover different exposure patterns:
- **Average exposure scenario** to mimic typical exposure
- **High exposure scenario**

暴露評価案: 全般的な方法

- **以下のようなEUの住民における評価**:
  - BPAに対する**慢性的**暴露
  - **異なる暴露源**(食事、感熱紙、空気、ほこり、おもちゃ、化粧品)
  - **異なる暴露経路**(食事由来、食事外経口、経皮、吸入)
  - **異なる年齢クラス**(もっとも弱者と見なされるグループ: 乳幼児、小児、妊娠可能年齢の女性(胎児及び母乳で育てられている乳幼児の暴露に対応するため)を含む)

- 各暴露源および各年齢クラスの間で異なる暴露パターンをカバーするため、それぞれの**暴露シナリオ**を作成した。
  - **平均的暴露シナリオ**: 典型的な暴露を模倣する
  - **高用量暴露シナリオ**

Potential sources and routes of exposure

		Route of exposure		
	Main examples	**Oral**	**Dermal**	**Inhalation**
Food and beverages	Migration from food packaging and water pipes	X		
	Migration from utensils (e.g. tableware)	X		
	Human milk and animal products (carry-over)	X		
	Food in general (contaminant?)	X		
Environmental media	Surface water (swimming)	X	X	
	Dust	X	X	X
	Indoor and outdoor air			X
Medical devices*	Dental fillings	X		
Consumer products	Cosmetics	X	X	
	Children's toys and teats	X	X	
	Thermal paper (e.g. bus tickets, cash receipts)	X	X	
	Recycled paper (e.g. toilet paper, kitchen paper)	X	X	

* SCENIHR of DG SANCO is currently reviewing the exposure to BPA via medical devices

暴露源となる可能性のあるもの及びその暴露経路

		暴露経路		
	主な例	**経口**	**経皮**	**吸入**
食品 飲料	食品の包装及び水道管からの移行	X		
	台所用品からの移行（例：食器）	X		
	ヒトの母乳及び畜産物（キャリーオーバー）	X		
	食品全般 （汚染物質？）	X		
環境媒介物	表層水（水泳）	X	X	
	ほこり	X	X	X
	室内外の空気			X
医療機器*	歯科充てん（填）用材料	X		
日用品	化粧品	X	X	
	小児用おもちゃ、おしゃぶり	X	X	
	感熱紙（例：バスの乗車券、レシート）	X	X	
	再生紙（例：トイレットペーパー、キッチンペーパー）	X	X	

* DG SANCOのSCENIHRが、現在、医療機器を介したBPAへの暴露の評価を行っている。

Draft exposure assessment: General approach

- **No assessment of:**
  - acute exposure
  - exposure in specific disease states
  - occupational exposure





暴露評価案: 全般的な方法

- **以下の評価は行わない:**
  - 急性暴露
  - 特定の病態における暴露
  - 職業上の暴露





Draft exposure assessment: General approach

Dietary exposure = concentration in food x food consumption

Non-dietary exposure = BPA concentration data in and from non-food sources x behaviour patterns to estimate non-dietary exposure.

Issues arising when combining exposures via various routes and from various sources

• The assumptions made should ensure a similar degree of conservativeness among the different sources to allow a comparison of the relative source contribution.

• It is inappropriate to sum up **external** exposures over different routes (oral, inhalation and dermal), because of the different route-dependent metabolism of BPA.

• **For each route**, average external exposures are calculated by summing up the average exposures from every source, and high external exposure by summing up the high exposures for every source by route.

•**Aggregated exposure from various routes** was calculated for risk assessment purposes after applying the **HED approach**

暴露評価案: 全般的な方法

食事由来の暴露 ＝ 食物中の濃度 X 食物摂取量

食事外由来の暴露 ＝ 食物外暴露源に含まれる、または由来するBPA 濃度データ X 行動パターンにより、食事外由来の暴露量を推計する。

異なる経路による暴露と、異なる暴露源に由来する暴露を合わせた時には、問題が生じる

• 暴露量の推定は、異なる暴露源の間で同じ程度の慎重さを確保して、それぞれの暴露源の関与を相対的に比較できるようにすべきである。

• 暴露経路の違いによってBPA代謝が異なるために、異なった経路による**外部暴露**(経口、吸入、経皮)を合算することは不適当である。

• **個々の暴露経路について**、平均外部暴露量は、全ての暴露源からの平均暴露量を合算して算出し、高暴露量はすべての暴露源からの高暴露量を経路ごとに合算する。

•**異なる経路からの総暴露量**をリスク評価の目的で計算する場合は、ヒト等価用量アプローチ(**HED アプローチ**)を適用した後に計算する。

Occurrence data

検出データ

Occurrence data sources for exposure assessment

Scientific literature
(public domain)

EFSA's Call for data

暴露評価のために使用したデータ・ソース

科学論文
(共有財産)

EFSAのデータ提供呼び掛け

Occurrence data in food from the literature

- All data **published** from **2006 to 2012**
- Only data for foods purchased or produced in **Europe** were considered.
- Occurrence data at the level of **individual samples** in the majority of cases.
- Only data fulfilling ***Quality criteria*** for the analytical methods were used for exposure calculation.
  e.g. Type of analytical method, recovery and repeatability of the method, LOD and/or LOQ, measures to avoid background contamination, etc

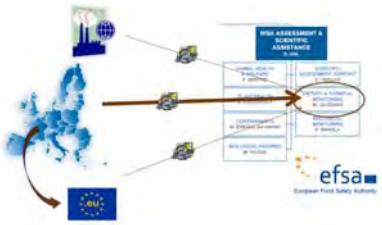
食品における検出に関する文献データ

- すべてのデータは**2006年から2012年までに文献報告されたもの。**
- **欧州において**購入もしくは製造された食品のデータのみを考慮。
- 検出データの大多数は、**個々の試料レベル**のデータである。
- 暴露量計算に用いたデータは、***品質基準***を満たした分析方法で検出されたデータのみを用いた。
  例えば、分析方法の種類、方法のリカバリーと繰り返し精度、LOD／LOQ、バックグラウンドへの混雑予防方法、等

Call for Bisphenol A occurrence data

- July 2012: EFSA launched a call to submit data on BPA
- Outcome: >1800 single data received

1) occurrence data in food & beverages for human consumption (ca. 290)
2) migration data from food contact materials (ca. 1000)
3) occurrence data in food contacts materials (ca. 600)



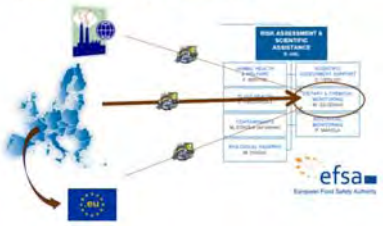
- Quality criteria as for other analytical data NOT applied

Draft exposure assessment

BPAの検出データの提供呼びかけ

- 2012年7月、EFSAはBPAのデータ提供の呼びかけを開始した。
- その結果、1800件以上のデータ提供が得られた。

1） ヒト食用及び飲用の食品及び飲料における検出データ （約290件）
2） 食品接触材料からの移行についてのデータ（約1000件）
3） 食品接触材料における検出データ （約600件）



- その他の分析データに関する品質基準は適用されなかった

Draft exposure assessment

Occurrence data in food - results

- Overall **2516** samples of food and beverages to assess BPA concentrations in the different food categories.
- For each food category: **BPA concentration data were merged from the literature and the call for data** as there were no major differences
- BPA concentrations: higher in canned vs non-canned food for most food categories
  - (BPA (Average: MB)>30 µg/kg in 7/17 canned foods, e.g. “Grain”, “Legumes/ nuts/ oilseeds”, “Meat”, “Fish/ seafood”, “Herbs, spices and condiments”, “Composite food”, and “Snacks, desserts, and other foods”).
- Average BPA levels are comparable for European vs non-European food

Draft exposure assessment

食品における検出データ – 結果

- 異なる食品カテゴリーにおけるBPA濃度の評価に、食品及び飲料合計2516サンプルを用いた.
- 文献及びデータ提供呼びかけから入手したBPA濃度に大きな違いはなかったので、暴露量データは、各食品カテゴリーごとにまとめた.
- ほとんどの食品カテゴリーにおいて、缶詰めされた食品に、缶詰めされていない食品より高いBPA濃度が検出された.
  缶詰め食品 17カテゴリー中7カテゴリー （「穀類」,「豆類/ナッツ/油糧種子」,「肉」,「魚/魚介類」,「ハーブ, スパイス及び香辛料」,「複合食品、スナック、デザート、その他食品」）において
  BPA (平均：MB) >30 µg/kgであった.
- 食品の平均BPAレベルは、欧州の食品と欧州以外の食品で同等だった.

Draft exposure assessment

Draft dietary exposure assessment

Food consumption

食事による暴露評価（案）

食品の摂取

Comprehensive Database: Adults & Children

EFSA Comprehensive European food consumption database

- Individual food consumption data from a total of 32 different surveys in 22 Member States provided to EFSA:
  - Covering > 67000 individuals
  - the most recent consumption data within the country
  - at the finest level of detail

包括データベース：成人および子供

ヨーロッパにおける食品摂取に関するEFSAの包括データベース：(DPPA/EFSA/DATEX/2008-2009)

- EU加盟22か国からEFSAに提供された32の異なる調査から得られた個人の食品摂取データ：
  - 67000人以上の個人をカバーしている
  - 国内における最新の食品摂取に関するデータ
  - 最も詳細なデータ

Age classes

The EFSA Comprehensive EU Food Consumption Database currently includes food consumption data for:

- Infants (0-12 months): 2 surveys in 2 countries,
- Toddlers (12-36 months): 8 surveys in 8 countries,
- Children (3-10 years): 16 surveys in 14 countries,
- Adolescents (10-18 years): 14 surveys in 12 countries,
- Adults (18-65 years) 21 surveys in 20 countries,
- Elderly (65-75 years): 9 surveys in 9 countries,
- Very elderly (>75 years): 8 surveys in 8 countries.

データベース年齢層

EUにおける食品摂取に関するEFSA包括データベースは、現在、以下の年齢層に関する食品摂取データを含む

- Infants (0-12 ヶ月): 2 調査 ／ 2 ヶ国
- Toddlers (12-36 ヶ月): 8 調査 ／ 8 ヶ国
- Children (3-10 歳): 16 調査 ／ 14 ヶ国
- Adolescents (10-18 歳): 14 調査 ／ 12 ヶ国
- Adults (18-65 歳) 21 調査 ／ 20 ヶ国
- Elderly (65-75 歳): 9 調査 ／ 9 ヶ国
- Very elderly (75 歳以上): 8 調査 ／ 8 ヶ国

Dietary exposure

- Based on a total of 2516 samples (scientific literature from 2006 onwards + EFSA call for data)
- **Average** exposure:
  - Average concentration in food x Average food consumption
- **High** exposure:
  - Average concentration in food x High food consumption

食事由来の暴露

- 2006年以降の科学論文調査およびEFSAのデータ募集で得た計2516件の資料に基づく
- 平均的暴露シナリオ:
  - 食品中の平均濃度 x 平均食品摂取量
- 高濃度暴露シナリオ:
  - 食品中の平均濃度 x 食品摂取量

ORAL (Average and High) exposure to BPA in the general population (ng/kg bw per day)

	Infants 0-6 months (breastfed)			Infants 0-6 months (formula fed)	Infants	Toddlers	Other children	Teenagers	Women	Men	Other adults	Elderly and very elderly
	1-5 days	6 days - 3 months	4 - 6 months	0- 6 months	6-12 months	1-3 years	3-10 years	10-18 years	18-45 years	18-45 years	45-65 years	65 years and over
Average Ingestion:												
Dust (average)		8.8	8.8	8.8	8.8	7.3	2.9	2.0	0.6	0.6	0.6	0.6
Toys (average)		0.3	0.3	0.3	0.3	0.02						
Dietary exposure from food and beverages (average)	225	180	158	30	375	375	290	159	132	126	126	116
Sum of all ingestion sources (AVERAGE)	225	189	168	39	384	382	293	161	132	127	127	117
High Ingestion:												
Dust (high)		14.6	14.6	14.6	14.6	12.2	4.9	3.3	1.0	1.0	1.0	1.0
Toys (high)		1.2	1.2	1.2	1.2	0.5						
Dietary exposure from food and beverages (high)	435	345	304	80	857	857	813	381	388	335	341	375
Sum of all ingestion sources (HIGH)	435	361	319	96	873	870	818	384	389	336	342	376

Exposure assessment

全ての集団におけるBPAの平均および高濃度経口暴露 (ng/kg bw per day)

	Infants 0-6 months (breastfed)			Infants 0-6 months (formula fed)	Infants	Toddlers	Other children	Teenagers	Women	Men	Other adults	Elderly and very elderly
	1-5 days	6 days - 3 months	4 - 6 months	0- 6 months	6-12 months	1-3 years	3-10 years	10-18 years	18-45 years	18-45 years	45-65 years	65 years and over
経口暴露による平均摂取												
Dust (average)		8.8	8.8	8.8	8.8	7.3	2.9	2.0	0.6	0.6	0.6	0.6
Toys (average)		0.3	0.3	0.3	0.3	0.02						
Dietary exposure from food and beverages (average)	225	180	158	30	375	375	290	159	132	126	126	116
Sum of all ingestion sources (AVERAGE)	225	189	168	39	384	382	293	161	132	127	127	117
経口暴露による高濃度摂取												
Dust (high)		14.6	14.6	14.6	14.6	12.2	4.9	3.3	1.0	1.0	1.0	1.0
Toys (high)		1.2	1.2	1.2	1.2	0.5						
Dietary exposure from food and beverages (high)	435	345	304	80	857	857	813	381	388	335	341	375
Sum of all ingestion sources (HIGH)	435	361	319	96	873	870	818	384	389	336	342	376

Exposure assessment

Non-dietary exposure

- The term “non-food sources” summarizes all sources that contribute to exposure via pathways other than the food pathway
  - Thermal paper
  - Indoor/ outdoor air (including air-borne dust)
  - Dust
  - Cosmetics
  - Toys and articles

食品以外からの暴露

「食品以外の暴露源」とは、以下に示す、食品を介した経路以外の経路を介して暴露するBPAのすべての暴露源を言う.

- 感熱紙
- 室内/屋外の空気（浮遊塵埃を含む）
- ほこり
- 化粧品
- 玩具や用品

Non-dietary exposure

- Analytical/experimental BPA concentration data in and from non-food sources were combined with behaviour patterns to estimate non-dietary exposure.

- For BPA Average exposure from non-food sources:
  - average values for all parameters (absorption rates and occurrence data) were chosen.

- For BPA High exposure from non-food sources:
  - same average values for all parameters but, as for dietary exposure, the frequency of use parameters was set to account for the highest 95th percentile among all EU countries.

食品以外からの暴露

食品以外からの暴露量を推定するため、食品以外の暴露源に含まれる、または由来するBPAについて、BPA濃度の分析値や実験値と行動パターンを併せて用いた.

- 食品外由来BPAの平均暴露量の推定には:
  - 全てのパラメーター(吸収率と検出データ)に平均値を用いた.

- 食品外由来BPAの高暴露量の推定には:
  - 全パラメーターに同じ平均値を用いたが、食事由来暴露と同様に、全EU加盟国中で最も高い95パーセンタイル値を計算するため、使用頻度のパラメーターを設定した.

AVERAGE exposure to BPA from all sources in the general population (ng/kg bw per day)

	Infants 0-6 months (breastfed)			Infants 0-6 months (formula fed)	Infants	Toddlers	Other children	Teenagers	Women	Men	Other adults	Elderly and very elderly
	1-5 days	6 days - 3 months	4 - 6 months	0- 6 months	6-12 months	1-3 years	3-10 years	10-18 years	18-45 years	18-45 years	45-65 years	65 years and over
Ingestion:												
Dust (average)		8.8	8.8	8.8	8.8	7.3	2.9	2.0	0.6	0.6	0.6	0.6
Toys (average)		0.3	0.3	0.3	0.3	0.02						
Dietary exposure from food and beverages (average)	225	180	158	30	375	375	290	159	132	126	126	116
Sum of all ingestion sources (average)	225	189	168	39	384	382	293	161	132	127	127	117
Inhalation:												
Air (average)	0.7	0.7	0.7	0.7	0.7	0.7	0.4	0.4	0.2	0.2	0.2	0.2
Sum of all inhalation sources (average)	0.7	0.7	0.7	0.7	0.7	0.7	0.4	0.4	0.2	0.2	0.2	0.2
Dermal:												
Thermal paper (average)*							69	94	59	59	59	59
Cosmetics (average)		4.8	4.8	4.8	4.8	2.8	2.2	2.5	2.0	2.0	2.0	2.0
Sum of all dermal sources (average)		4.8	4.8	4.8	4.8	2.8	71	96	61	61	61	61

全ての暴露源由来のBPA暴露量の平均 (ng/kg bw per day)

	Infants 0-6 months (breastfed)			Infants 0-6 months (formula fed)	Infants	Toddlers	Other children	Teenagers	Women	Men	Other adults	Elderly and very elderly
	1-5 days	6 days - 3 months	4 - 6 months	0- 6 months	6-12 months	1-3 years	3-10 years	10-18 years	18-45 years	18-45 years	45-65 years	65 years and over
Ingestion:												
Dust (average)		8.8	8.8	8.8	8.8	7.3	2.9	2.0	0.6	0.6	0.6	0.6
Toys (average)		0.3	0.3	0.3	0.3	0.02						
Dietary exposure from food and beverages (average)	225	180	158	30	375	375	290	159	132	126	126	116
Sum of all ingestion sources (average)	225	189	168	39	384	382	293	161	132	127	127	117
Inhalation:												
Air (average)	0.7	0.7	0.7	0.7	0.7	0.7	0.4	0.4	0.2	0.2	0.2	0.2
Sum of all inhalation sources (average)	0.7	0.7	0.7	0.7	0.7	0.7	0.4	0.4	0.2	0.2	0.2	0.2
Dermal:												
Thermal paper (average)*							69	94	59	59	59	59
Cosmetics (average)		4.8	4.8	4.8	4.8	2.8	2.2	2.5	2.0	2.0	2.0	2.0
Sum of all dermal sources (average)		4.8	4.8	4.8	4.8	2.8	71	96	61	61	61	61

HIGH exposure to BPA from all sources in the general population (ng/kg bw per day)

	Infants 0-6 months (breastfed)			Infants 0-6 months (formula fed)	Infants	Toddlers	Other children	Teenagers	Women	Men	Other adults	Elderly and very elderly
	1-5 days	6 days - 3 months	4 - 6 months	0- 6 months	6-12 months	1-3 years	3-10 years	10-18 years	18-45 years	18-45 years	45-65 years	65 years and over
Ingestion:												
Dust (high)		14.6	14.6	14.6	14.6	12.2	4.9	3.3	1.0	1.0	1.0	1.0
Toys (high)		1.2	1.2	1.2	1.2	0.5						
Dietary exposure from food and beverages (high)	435	345	304	80	857	857	813	381	388	335	341	375
Sum of all ingestion sources (high)	435	361	319	96	873	870	818	384	389	336	342	376
Inhalation:												
Air (high)	1.4	1.4	1.4	1.4	1.4	1.1	0.6	0.6	0.3	0.3	0.3	0.3
Sum of all inhalation sources (high)	1.4	1.4	1.4	1.4	1.4	1.1	0.6	0.6	0.3	0.3	0.3	0.3
Dermal:												
Thermal paper (high)*							550	863	542	542	542	542
Cosmetics (high)		9.4	9.4	9.4	9.4	5.5	4.2	4.8	4.0	4.0	4.0	4.0
Sum of all dermal sources (high)		9.4	9.4	9.4	9.4	5.5	554	868	546	546	546	546

全ての暴露源由来のBPA高暴露量 (ng/kg bw per day)

	Infants 0-6 months (breastfed)			Infants 0-6 months (formula fed)	Infants	Toddlers	Other children	Teenagers	Women	Men	Other adults	Elderly and very elderly
	1-5 days	6 days - 3 months	4 - 6 months	0- 6 months	6-12 months	1-3 years	3-10 years	10-18 years	18-45 years	18-45 years	45-65 years	65 years and over
Ingestion:												
Dust (high)		14.6	14.6	14.6	14.6	12.2	4.9	3.3	1.0	1.0	1.0	1.0
Toys (high)		1.2	1.2	1.2	1.2	0.5						
Dietary exposure from food and beverages (high)	435	345	304	80	857	857	813	381	388	335	341	375
Sum of all ingestion sources (high)	435	361	319	96	873	870	818	384	389	336	342	376
Inhalation:												
Air (high)	1.4	1.4	1.4	1.4	1.4	1.1	0.6	0.6	0.3	0.3	0.3	0.3
Sum of all inhalation sources (high)	1.4	1.4	1.4	1.4	1.4	1.1	0.6	0.6	0.3	0.3	0.3	0.3
Dermal:												
Thermal paper (high)*							550	863	542	542	542	542
Cosmetics (high)		9.4	9.4	9.4	9.4	5.5	4.2	4.8	4.0	4.0	4.0	4.0
Sum of all dermal sources (high)		9.4	9.4	9.4	9.4	5.5	554	868	546	546	546	546

Conclusions – Draft dietary exposure

- **Age groups with highest estimated dietary** intake of BPA: **infants > 6 months and toddlers (1-3 yrs)**
  - **Average**: 375 ng/kg bw/day;
  - **High**: 857 ng/kg bw/day
- **Current** estimated dietary exposure to BPA is far **lower than** that estimated by EFSA **in 2006** (up to 5300 ng/kg bw/day in toddlers).
- Reason: lack of data and very conservative assumptions in 2006

結論－食事由来の暴露（案）

- 食事経由の推定BPA摂取量が最も高い年齢層
  生後6か月より大きい乳児及び幼児（1～3歳児）
  - 平均：375 ng/kg bw/day
  - 最高：857 ng/kg bw/day
- 食事経由のBPA暴露量の現在の推定値は、2006年にEFSAが発表した推定値（幼児で、最高5300 ng/kg bw/day）よりもはるかに低い.
- 理由：2006年の時点ではデータが不足していたこと、及び当時の推定が非常に慎重なものであったことによる.

Conclusions – Draft non-dietary exposure

- **Main non-food source**: thermal paper for children >3 years, teenagers and adults
  - **Average**: 69, 94 and 59 ng/kg bw/day
  - **High**: 550, 863 and 542 ng/kg bw/day
- **Average** values for thermal paper differed by a **factor of 10** from the respective **high values**.
  - due to *highly conservative assumptions*, e.g., frequency and number of fingers handling thermal paper, when assessing high exposure
- BPA exposure via dust, cosmetics and indoor air was less important

結論－食事以外の由来による暴露（案）

- 食品以外の主な暴露源：感熱紙
- 年齢層別の暴露量；
  - 3歳より大きい子供（平均： 69 ng/kg bw/d; 最高： 550 ng/kg bw/d）
  - ティーンエイジャー（平均： 94 ng/kg bw/d; 最高： 863 ng/kg bw/d）
  - 成人（平均： 59 ng/kg bw/d; 最高： 542 ng/kg bw/d）
- 感熱紙由来の暴露量推定値では、平均値と最高値で10倍の開きがある．これは、感熱紙を扱う頻度と接触する指の数を非常に慎重に推定して、最高暴露量を推定したためである．
- ほこり、化粧品及び屋内の空気を経由したBPA暴露は、無視できるほど低い。

Draft assessment of human health risks

- Draft exposure assessment
  - Dietary exposure
  - Non-dietary exposure

- Draft assessment of human health risks
  - Hazard identification (HI)
    - Weight of evidence (WoE) approach to identify “likely” effects
  - Hazard characterisation (HC) for likely effects
    - BMD modelling
    - HED approach
  - Risk characterisation (RC)

ヒトの健康影響リスクの評価（案）

- 暴露評価（案）
  - 食事由来の暴露
  - 食事由来でない暴露

- ヒトの健康影響リスクの評価案
  - 危害要因の特定(HI)
    - 「起こる可能性のある」影響を特定するための、証拠の重み付け（Weight of evidence, WoE） を用いた方法
  - 起こる可能性のある影響についての危害要因の判定(HC)
    - ベンチマークドーズモデル
    - ヒト等価用量（HED）アプローチ
  - リスクの判定(RC)

Sources of studies for hazard identification and characterisation

MAIN study sources
NEW studies (human, animal and in vitro) retrieved via a comprehensive literature search for the period August 2010-December 2012[1]
NEW relevant studies published in 2013 (on a case by case basis)
Previously identified **KEY studies** for BPA toxicological assessment by EFSA (2006; 2010) or other risk assessment bodies
In vitro and in vivo studies on **genotoxicity** published **after the 2006** EFSA opinion
EARLIER studies not considered in the EFSA Opinion of 2010, because they did not match the inclusion criteria established at the time, e.g. non oral studies, exposure during adult age, single dose

危害要因の特定と判定の基となる調査研究

基となる主な調査研究
2010年8月～2012年12月の間に行われた包括的文献調査によって検索された**新しい研究**（ヒト、動物、*in vitro*）
2013年に発表された**新規の関連研究**（個別に判断）
過去のEFSA(2006; 2010)やその他のリスク評価機関によるPAの毒性評価において、**重要な研究**と認定された研究
2006年のEFSAの意見書の後に発表された、**遺伝毒性**に関する *in vitro* および *in vivo* 研究
2010年のEFSAの意見書において、当時設定された選定基準を満たさずに考慮されなかった**過去の研究** **例：非経口投与による研究、成長後の暴露、単回投与**

Study selection criteria

Inclusion of:

- **primary peer-reviewed research studies** in English dealing with human/animal/in vitro toxicity of BPA (no other BPA forms/ metabolites or mixtures, or ecotoxicity);
- **Reviews** (only as a source of studies)

- Human studies
  - **Biomonitoring** studies and **epidemiological** studies, **ex vivo** studies
  - All routes of exposure (also non-oral routes);

- Animal toxicity studies
  - including **non-oral** routes of exposure and **single dose** studies (for supporting evidence to HI):
  - For **reproductive** and developmental toxicity studies, only “low dose studies” (at least one dose below the oral human equivalent dose (HED) of 3.6 mg BPA/kg bw per day)

研究の選定基準

選定される研究論文

- BPA の ヒト／動物／*in vitro* における毒性に関して、英語で書かれ、**専門家の査読を経た研究論文**.（他のBPA構造物質／代謝物または混合物、または環境毒性に関する研究は含まず）
- **総説・解説**（調査の基となる資料としてのみ）

- ヒトでの研究
  - **バイオモニタリング**研究、**疫学調査**、*ex vivo* **研究**
  - 全ての経路による暴露（非経口を含む);

- 動物実験による毒性試験
  - **非経口**暴露による**単回**投与試験を含む（危害要因特定の根拠として):
  - **繁殖**毒性および発達毒性については、“低用量”（ヒト等価用量(HED)3.6 mg BPA/kg bw per dayよりも低い用量の投与群を、少なくとも1群は含む)の試験研究に限る。

Macro-areas by which the relevant studies for BPA HI were grouped and their consideration

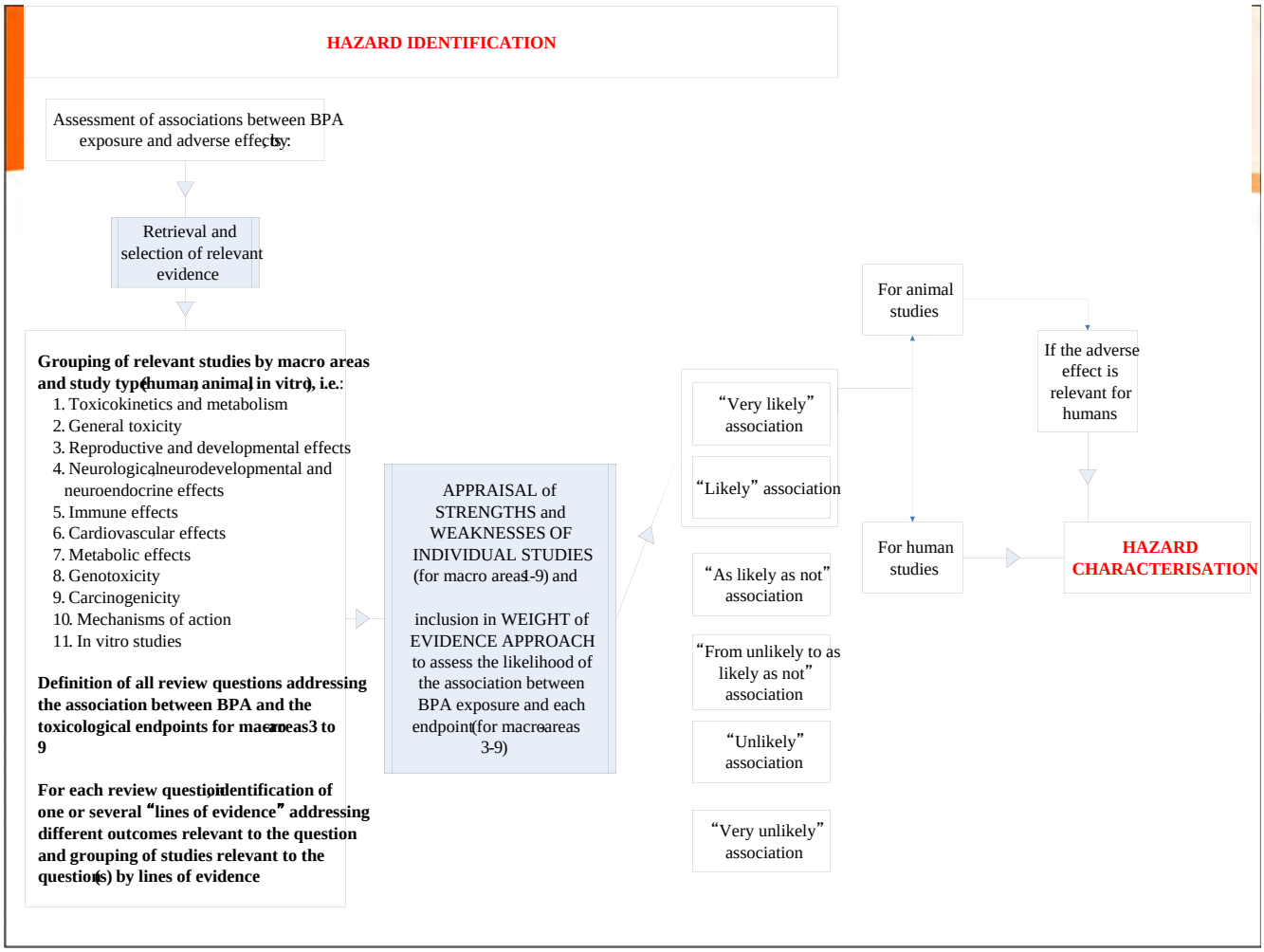
Study content	How the study was considered
1. Toxicokinetics & metabolism (human & animal studies) 2. General toxicity (animal studies)	-Appraisal of strengths and weaknesses
3. Reproductive & developmental effects (human & animal studies) 4. Neurotoxicity (human & animal studies) 5. Immune effects (human & animal studies) 6. Cardiovascular effects (human & animal studies) 7. Metabolic effects (human & animal studies) 8. Genotoxicity (in vitro & in vivo studies) 9. Carcinogenicity (human & animal studies)	-Appraisal of strengths and weaknesses + -Inclusion in the Weight of Evidence (WoE) approach to hazard identification
10. Mechanisms of action of BPA (including epigenetics & gene expression studies) 11. In vitro studies (only if < 100 nM)	-Use as supplementary information for the toxicological evaluation

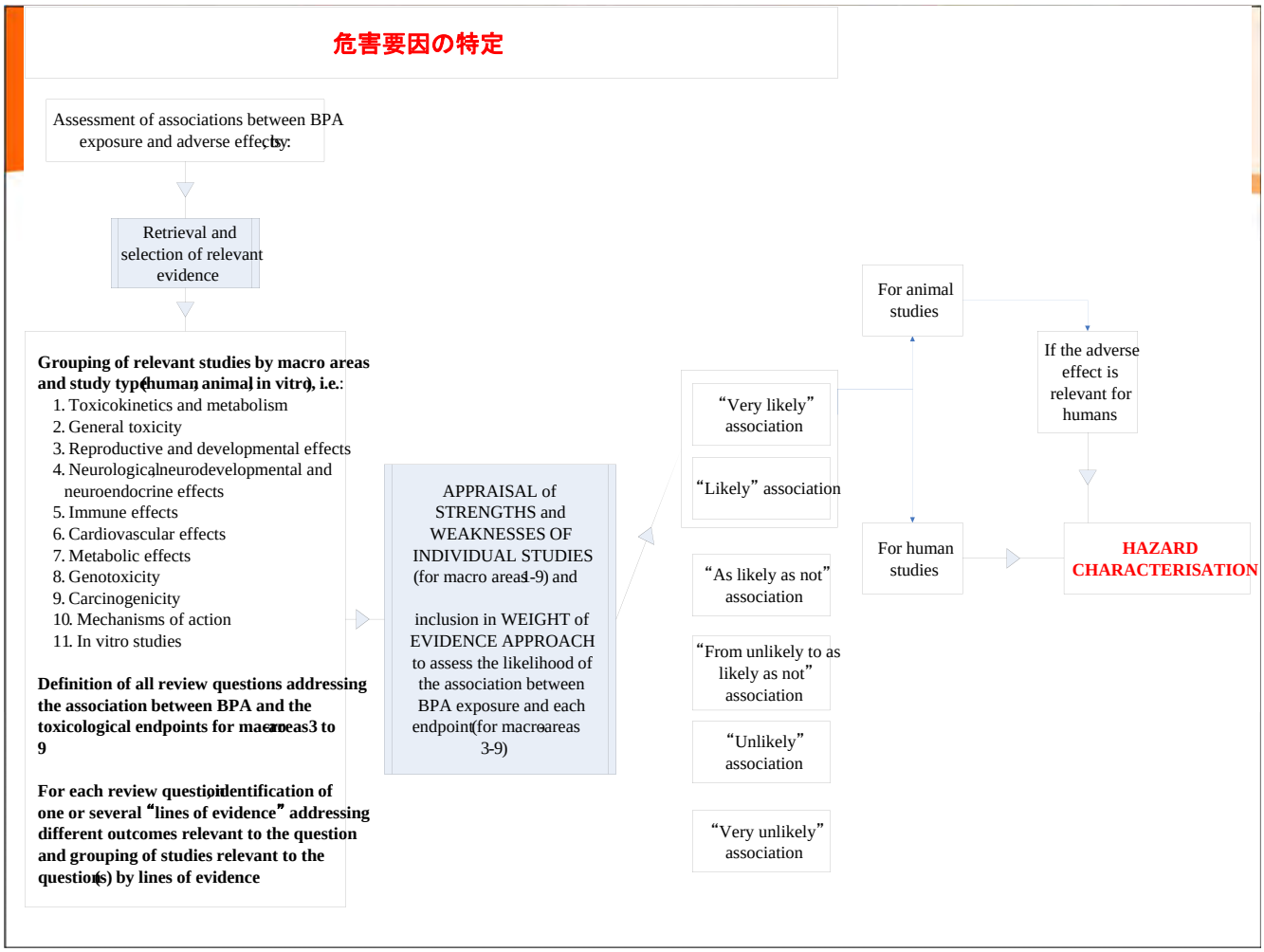
Hazard identification

BPAの危害要因特定の基になる関連研究分野とそれぞれの評価

研究の内容	研究の評価点
1. トキシコキネティクス及び代謝（ヒトおよび動物） 2. 一般毒物学（動物）	長所と短所を評価
3. 生殖・発生への影響（ヒトおよび動物） 4. 神経毒性（ヒトおよび動物） 5.免疫系への影響（ヒトおよび動物） 6.心血管系への影響（ヒトおよび動物） 7.代謝への影響（ヒトおよび動物） 8.遺伝毒性（*in vitro* 及び *in vivo*） 9.発がん性（ヒトおよび動物）	−長所と短所を評価 ＋ −危害要因の特定に用いるWoE アプローチ（証拠の重み付け）に含める.
10. BPAの作用機序(エピジェネティクス及び遺伝子発現研究を含む） 11. *In vitro* 研究 （100 nM 未満の低用量の場合のみ）	−毒物学的評価のための追加情報として用いる.

Hazard identification


HAZARD IDENTIFICATION
Assessment of associations between BPA exposure and adverse effects by:
Retrieval and selection of relevant evidence
Grouping of relevant studies by macro areas and study type (human, animal, in vitro), i.e.:
1. Toxicokinetics and metabolism
2. General toxicity
3. Reproductive and developmental effects
4. Neurological, neurodevelopmental and neuroendocrine effects
5. Immune effects
6. Cardiovascular effects
7. Metabolic effects
8. Genotoxicity
9. Carcinogenicity
10. Mechanisms of action
11. In vitro studies
Definition of all review questions addressing the association between BPA and the toxicological endpoints for macro areas 3 to 9
For each review question, identification of one or several "lines of evidence" addressing different outcomes relevant to the question and grouping of studies relevant to the question(s) by lines of evidence
APPRAISAL of STRENGTHS and WEAKNESSES OF INDIVIDUAL STUDIES (for macro areas 1-9) and
inclusion in WEIGHT of EVIDENCE APPROACH to assess the likelihood of the association between BPA exposure and each endpoint (for macro areas 3-9)
"Very likely" association
"Likely" association
"As likely as not" association
"From unlikely to as likely as not" association
"Unlikely" association
"Very unlikely" association
For animal studies
If the adverse effect is relevant for humans
For human studies
HAZARD CHARACTERISATION


危害要因の特定
Assessment of associations between BPA exposure and adverse effects by:
Retrieval and selection of relevant evidence
Grouping of relevant studies by macro areas and study type (human, animal, in vitro), i.e.:
1. Toxicokinetics and metabolism
2. General toxicity
3. Reproductive and developmental effects
4. Neurological, neurodevelopmental and neuroendocrine effects
5. Immune effects
6. Cardiovascular effects
7. Metabolic effects
8. Genotoxicity
9. Carcinogenicity
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"Very likely" association
"Likely" association
"As likely as not" association
"From unlikely to as likely as not" association
"Unlikely" association
"Very unlikely" association
For animal studies
If the adverse effect is relevant for humans
For human studies
HAZARD CHARACTERISATION

Hazard identification - Weight of evidence (WoE) approach

- A structured WoE approach was applied to facilitate the consistent treatment of the evidence and document it in a tabular format for transparency
- **Review Questions** were asked for each toxicological endpoint relevant for hazard identification of BPA
- For each question, a starting point (based on EFSA previous evaluations) was identified and the new relevant publications were organised into a number of "**lines of evidence**".
- The **strengths and weaknesses** of each line of evidence were briefly summarised, to facilitate a conclusion to be drawn on the likelihood that exposure to BPA was associated with a particular effect.

危害要因の特定- 証拠の重み付け(WoE) アプローチ

- 危害要因の証拠の一貫した処理を容易にするために、体系的な証拠の重み付けを行い（WoE）、それを表形式にまとめて透明性を高めた.
- BPAの危害要因特定にとって重要な各毒性学的エンドポイントについて、それぞれ**再評価のための質問**を行った.
- 各質問に対して、EFSAによる前回評価に基づいて起点を特定し、関連する新しい論文をいくつかの**"lines of evidence（一連の証拠）"**にまとめて整理した.
- BPA暴露が特定の影響と関連する可能性に関して結論を出しやすくするために、各**line of evidence**について証拠としての**長所と短所**を要約した.

WoE table in hazard identification

Example of table used in the WoE approach

Question 1: Is BPA……..?	Answer to the question as reported by the study authors (Positive, Negative or Uncertain)	Reliability of evidence (Low, Medium or High)	Influence on Likelihood
Starting point: e.g. conclusions of the 2010 EFSA opinion. *Strengths:* *Weaknesses:*			
Line of Evidence 1: new evidence on.. *Strengths:* *Weaknesses:*			
Line of Evidence 2: increased effect on…… *Strengths:* *Weaknesses:*			
Overall conclusion on Likelihood:			Chosen likelihood level

危害要因の特定に用いた「証拠の重み付け」表

「証拠の重み付け」に用いた表の例

質問1: Is BPA……..?	質問に対する著者の回答 (Positive, Negative or Uncertain)	証拠の信頼性 (Low, Medium or High)	各質問に対して回答がpositiveである可能性に与える影響
Starting point: e.g. conclusions of the 2010 EFSA opinion. *Strengths:* *Weaknesses:*			
Line of Evidence 1: new evidence on.. *Strengths:* *Weaknesses:*			
Line of Evidence 2: increased effect on…… *Strengths:* *Weaknesses:*			
Overall conclusion on Likelihood:			選択された可能性のレベル

WOE questions

- **Questions are asked for each toxicological endpoint relevant for BPA.**

Example: Is BPA carcinogenic in animals when exposed during their adult life (post-pubertal) only?

Question 1: Is BPA carcinogenic in animals when exposed during their adult life (post-pubertal) only?	Answer to the question as reported by the study authors (Positive, Negative or Uncertain)	Reliability of evidence (Low, Medium or High)	Influence on Likelihood
Starting point based on previous assessments (EFSA, 2006; 2010): ***Strengths:*** ***Weaknesses:***			
Line of Evidence x: new evidence on ……. ***Strengths:*** ***Weaknesses:***			

WOEでの質問

BPAに関係する各毒性学的エンドポイントについて質問を設定

例: BPAは動物において、成体の期間のみ暴露された場合に発がん性があるか?

Question 1: Is BPA carcinogenic in animals when exposed during their adult life (post-pubertal) only?	Answer to the question as reported by the study authors (Positive, Negative or Uncertain)	Reliability of evidence (Low, Medium or High)	Influence on Likelihood
Starting point based on previous assessments (EFSA, 2006; 2010): ***Strengths:*** ***Weaknesses:***			
Line of Evidence x: new evidence on ……. ***Strengths:*** ***Weaknesses:***			

WOE Starting point

- **The conclusions from the EFSA opinions on BPA of 2006 and/or 2010 were taken as starting point for answering each question.**

Example: BPA did not show any significant carcinogenic activity in 2 standard oral cancer bioassays in rats and mice (NTP 1982)

Question 1: Is BPA carcinogenic in animals when exposed during their adult life (post-pubertal) only?	Answer to the question as reported by the study authors (Positive, Negative or Uncertain)	Reliability of evidence (Low, Medium or High)	Influence on Likelihood
Starting point based on previous assessments (EFSA, 2006; 2010): BPA did not show any significant carcinogenic activity in 2 standard oral cancer bioassays in rats and mice (NTP 1982)			

WOEの起点

BPAに関するEFSAの科学的意見書（2006年／2010年）からの結論を、WOEの各質問に対する回答の起点とする.

例: ラット及びマウスに標準的経口投与を行った2例のがんバイオアッセイにおいて、BPAは何ら有意な発がん性を示さなかった（NTP 1982）

Question 1: Is BPA carcinogenic in animals when exposed during their adult life (post-pubertal) only?	Answer to the question as reported by the study authors (Positive, Negative or Uncertain)	Reliability of evidence (Low, Medium or High)	Influence on Likelihood
Starting point based on previous assessments (EFSA, 2006; 2010): BPA did not show any significant carcinogenic activity in 2 standard oral cancer bioassays in rats and mice (NTP 1982)			

WOE line of evidence

- **The new evidence that is relevant to each question is organised into a number of lines of evidence** (from one or more publications)

Example: Effects on tumour induction in adult life (Jenkins et al., 2011)

Question 1: Is BPA carcinogenic in animals when exposed during their adult life (post-pubertal) only?	Answer to the question as reported by the study authors (Positive, Negative or Uncertain)	Reliability of evidence (Low, Medium or High)	Influence on Likelihood
Starting point based on previous assessments (EFSA, 2006; 2010): ***Strengths:....etc***			
Line of Evidence 1: **Effects on tumour induction in adult life (Jenkins et al., 2011)** ***Strengths:*** ***Weaknesses:***			

WOEにおけるline of evidence

- **各質問に関連する新しい証拠は、根拠となる一報又はそれ以上の論文からの、いくつかのline of evidenceに整理される**

例: 成体における腫瘍誘発作用に対する影響（Jenkins et al., 2011）

Question 1: Is BPA carcinogenic in animals when exposed during their adult life (post-pubertal) only?	Answer to the question as reported by the study authors (Positive, Negative or Uncertain)	Reliability of evidence (Low, Medium or High)	Influence on Likelihood
Starting point based on previous assessments (EFSA, 2006; 2010): ***Strengths:....etc***			
Line of Evidence 1: **Effects on tumour induction in adult life (Jenkins et al., 2011)** ***Strengths:*** ***Weaknesses:***			

WOE: strengths and weaknesses

- **The strengths and weaknesses of each line of evidence are briefly summarised**

Example: ***Weaknesses:*** Insufficient data reporting (e.g. on tumour incidence, incomplete histopathology, time of necropsy not defined)

Question 1: Is BPA carcinogenic in animals when exposed during their adult life (post-pubertal) only?	**Answer to the question as reported by the study authors (Positive, Negative or Uncertain)**	**Reliability of evidence (Low, Medium or High)**	**Influence on Likelihood**
Starting point based on previous assessments……			
Line of Evidence 1: Effects on tumour induction in adult life (Jenkins et al., 2011) ***Strengths:*** -number of doses, large sample size, soy-free diet, etc. ***Weaknesses:*** -insufficient data reporting (e.g. on tumour incidence, incomplete histopathology, time of necropsy not defined)			

WOE：証拠としての「長所・短所」

- **各line of evidenceの長所と短所について、短く要約する.**

例: **短所**: 不完全なデータの報告である（たとえば、腫瘍発生率については、組織病理学的検査が不完全, 剖検時間が特定されていない　など）

Question 1: Is BPA carcinogenic in animals when exposed during their adult life (post-pubertal) only?	**Answer to the question as reported by the study authors (Positive, Negative or Uncertain)**	**Reliability of evidence (Low, Medium or High)**	**Influence on Likelihood**
Starting point based on previous assessments……			
Line of Evidence 1: Effects on tumour induction in adult life (Jenkins et al., 2011) ***Strengths:*** -number of doses, large sample size, soy-free diet, etc. ***Weaknesses:*** -insufficient data reporting (e.g. on tumour incidence, incomplete histopathology, time of necropsy not defined)			

WOE: direction of evidence

- **Direction of the line of evidence (study author's view)** (descriptive as positive, negative or uncertain. Or for example "mainly negative")

Question 1: Is BPA carcinogenic in animals when exposed during their adult life (post-pubertal) only?	Answer to the question as reported by the study authors (Positive, Negative or Uncertain)	Reliability of evidence (Low, Medium or High)	Influence on Likelihood
Starting point based on previous assessments…… **BPA did not show any significant carcinogenic activity in 2 standard oral cancer bioassays in rats and mice (NTP 1982)**	**Mainly negative**		
Line of Evidence 1: Effects on tumour induction in adult life (Jenkins et al., 2011) ***Strengths:*** -number of doses, large sample size, soy-free diet, etc.	**Positive**		

WOE: 証拠の示唆する"方向"

- **line of evidenceの方向性(論文著者の見解)**

(肯定、否定又は不確実と記述される。又は "主にネガティブ"と 記述される。)

Question 1: Is BPA carcinogenic in animals when exposed during their adult life (post-pubertal) only?	Answer to the question as reported by the study authors (Positive, Negative or Uncertain)	Reliability of evidence (Low, Medium or High)	Influence on Likelihood
Starting point based on previous assessments…… **BPA did not show any significant carcinogenic activity in 2 standard oral cancer bioassays in rats and mice (NTP 1982)**	**Mainly negative**		
Line of Evidence 1: Effects on tumour induction in adult life (Jenkins et al., 2011) ***Strengths:*** -number of doses, large sample size, soy-free diet, etc. ***Weaknesses:*** -insufficient data reporting (e.g. on tumour incidence, incomplete histopathology, time of necropsy not defined)	**Positive**		

WOE: reliability

- **Reliability expresses the Panel's assessment of the likelihood that the reported results or findings are real or valid** (low, medium or high)

Question 1: Is BPA carcinogenic in animals when exposed during their adult life (post-pubertal) only?	Answer to the question as reported by the study authors (Positive, Negative or Uncertain)	Reliability of evidence (Low, Medium or High)	Influence on Likelihood
Starting point based on previous assessments…… **BPA did not show any significant carcinogenic activity in 2 standard oral cancer bioassays in rats and mice (NTP 1982)**	**Mainly negative**	**Medium**	
Line of Evidence 1: Effects on tumour induction in adult life (Jenkins et al., 2011) ***Strengths:*** -number of doses, large sample size, soy-free diet, etc	**Positive**	**Low**	

WOE: 証拠の信頼性

- 「証拠の信頼性」欄には、報告された結果または知見が事実であるか又は価値があるかどうかの可能性について、専門パネルの評価を記載する.

記載例：信頼性（低い、中程度、高い）

Question 1: Is BPA carcinogenic in animals when exposed during their adult life (post-pubertal) only?	Answer to the question as reported by the study authors (Positive, Negative or Uncertain)	Reliability of evidence (Low, Medium or High)	Influence on Likelihood
Starting point based on previous assessments…… **BPA did not show any significant carcinogenic activity in 2 standard oral cancer bioassays in rats and mice (NTP 1982)**	**Mainly negative**	**Medium**	
Line of Evidence 1: Effects on tumour induction in adult life (Jenkins et al., 2011) ***Strengths:*** -number of doses, large sample size, soy-free diet, etc. ***Weaknesses:*** -insufficient data reporting (e.g. on tumour incidence, …)	**Positive**	**Low**	

WOE: influence on likelihood

- **The answer to the question and reliability were taken into account when judging the influence of each line of evidence on the likelihood of the proposition under assessment**

Pairs of symbols indicate uncertainty about the influence, e.g. ●/↑ = between negligible and minor positive influence on likelihood

Question 1: Is BPA carcinogenic in animals when exposed during their adult life (post-pubertal) only?	Answer to the question as reported by the study authors (Positive, Negative or Uncertain)	Reliability of evidence (Low, Medium or High)	Influence on Likelihood
Starting point based on previous assessments…… **BPA did not show any significant carcinogenic activity in 2 standard oral cancer bioassays in rats and mice (NTP 1982)**	**Mainly negative**	**Medium**	↓↓
Line of Evidence 1: Effects on tumour induction in adult life (Jenkins et al., 2011) ***Strengths:*** -number of doses, large sample size, soy-free diet, etc.	**Positive**	**Low**	●/↑

WOE：可能性の判定への影響

- **専門パネルは、各line of evidenceが評価中の提案（質問事項）の可能性に影響を与えるかどうかを判定する際に、質問への回答と証拠の信頼性を考慮した.**

二つの記号の組み合わせは、影響の不確実性を示す,
例, ●/↑ = 可能性が「無視できる」と「わずかに陽性」の間

Question 1: Is BPA carcinogenic in animals when exposed during their adult life (post-pubertal) only?	Answer to the question as reported by the study authors (Positive, Negative or Uncertain)	Reliability of evidence (Low, Medium or High)	Influence on Likelihood
Starting point based on previous assessments…… **BPA did not show any significant carcinogenic activity in 2 standard oral cancer bioassays in rats and mice (NTP 1982)**	**Mainly negative**	**Medium**	↓↓
Line of Evidence 1: Effects on tumour induction in adult life (Jenkins et al., 2011) ***Strengths:*** -number of doses, large sample size, soy-free diet, etc. ***Weaknesses:*** -insufficient data reporting (e.g. on tumour incidence, …)	**Positive**	**Low**	●/↑

Symbols used for expressing influence on likelihood for each line of evidence

Table . Definition of symbols used for expressing the influence of each line of evidence on likelihood in the WoE tables.

Symbols	Interpretation
↑	minor contribution to increasing likelihood
↑↑	moderate contribution to increasing likelihood
↑↑↑	major contribution to increasing likelihood
↓	minor contribution to decreasing likelihood
↓↓	moderate contribution to decreasing likelihood
↓↓↓	major contribution to decreasing likelihood
●	negligible influence on likelihood
?	unable to evaluate influence on likelihood

Hazard identification

Pairs of symbols indicate uncertainty about the influence,
e.g., ●/↑ = between negligible and minor positive influence on likelihood

各line of evidenceが可能性に及ぼす影響を表すシンボル

WoE表で各line of evidenceが可能性に及ぼす影響を表すシンボルの意味

シンボル	意味
↑	可能性の増大に対して寄与は小さい
↑↑	可能性の増大に対して中程度に寄与する
↑↑↑	可能性の増大に対して大きく寄与する
↓	可能性の低下に対して寄与は小さい
↓↓	可能性の低下に対して中程度に寄与する
↓↓↓	可能性の低下に対して大きく寄与する
•	可能性への影響は無視できる
?	可能性への影響は評価できない

Hazard identification

二つの記号の組み合わせは、影響の不確実性を示す,
例, ●/↑ = 可能性が「無視できる」と「わずかに陽性」の間

WOE: overall conclusions on likelihood

- **Example for carcinogenicity after adult exposure**

Question 1: Is BPA carcinogenic in animals when exposed during their adult life (post-pubertal) only?	Answer to the question as reported by the study authors (Positive, Negative or Uncertain)	Reliability of evidence (Low, Medium or High)	Influence on Likelihood
Starting point based on previous assessments…… BPA did not show any significant carcinogenic activity in 2 standard oral cancer bioassays in rats and mice (NTP 1982)	Mainly negative	Medium	↓↓
Line of Evidence 1: Effects on tumour induction in adult life (Jenkins et al., 2011)	Positive	Low	●/↑
Line of evidence 2: effects on tumour induction in the prostate (Prins et al., 2011)	Positive	Low	●
Overall conclusion on carcinogenicity of BPA in animals when exposed during their adult life (post-pubertal) only: Effects on mammary gland growth demonstrated in a transgenic mouse model with post-pubertal exposure (Jenkins et al., 2011) or on prostatic "intraepithelial neoplasia" in rats exposed to BPA in the immediate postnatal period (Prins et al. 2011) do not provide convincing evidence that BPA is carcinogenic in animals when exposed postnatally/during their adult life.			**Unlikely to as likely as not**

Overall likelihood

WOE: 可能性に関する総合的結論

- **例：生体への暴露による発がん性について**

Question 1: Is BPA carcinogenic in animals when exposed during their adult life (post-pubertal) only? **質問1：BPAは動物において、成体の期間のみ暴露された場合に発がん性があるか?**	Answer to the question as reported by the study authors (Positive, Negative or Uncertain)	Reliability of evidence (Low, Medium or High)	Influence on Likelihood
Starting point based on previous assessments…… BPA did not show any significant carcinogenic activity in 2 standard oral cancer bioassays in rats and mice (NTP 1982)	Mainly negative	Medium	↓↓
Line of Evidence 1: Effects on tumour induction in adult life (Jenkins et al., 2011)	Positive	Low	●/↑
Line of evidence 2: effects on tumour induction in the prostate (Prins et al., 2011)	Positive	Low	●
Overall conclusion on carcinogenicity of BPA in animals when exposed during their adult life (post-pubertal) only: Effects on mammary gland growth demonstrated in a transgenic mouse model with post-pubertal exposure (Jenkins et al., 2011) or on prostatic "intraepithelial neoplasia" in rats exposed to BPA in the immediate postnatal period (Prins et al. 2011) do not provide convincing evidence that BPA is carcinogenic in animals when exposed postnatally/during their adult life.			**Unlikely to as likely as not**

総合的な可能性

Definitions of terms used for expressing overall likelihood

- **The overall assessment of likelihood, taking into account all lines of evidence and any dependencies between them, is expressed using a 6 degree scale of verbal terms.**

Definition of terms used for expressing likelihood
Very likely
Likely
As likely as not
From unlikely to as likely as not
Unlikely
Very unlikely

総合的な可能性の表記に使う用語の定義

可能性の総合的評価は、全てのline of evidenceと相互の依存性を考慮したうえで、6段階に分けて表に示した用語で記載する.

可能性の表記に用いる用語の定義
Very likely　可能性は大変高い
Likely　　可能性があるだろう
As likely as not　どちらとも言えない
From unlikely to as likely as not　　Unlikely か、どちらとも言えないかの間
Unlikely　　可能性はないだろう
Very unlikely　可能性は大変低い

WoE: Example for mammary proliferation (without strengths and weaknesses)

Q2: Does BPA induce proliferative changes in the mammary gland of animals exposed during pre- and/or post-natal (during lactation) development or up to PND 90 (gavage)?	Answer to the question by the study authors (Positive, Negative or Uncertain)	Reliability of evidence (Low, Medium or High)	Influence on Likelihood (see Table 28)
Starting point based on previous assessments (EFSA, 2006, 2010): Based on the reviewed studies the implications of cell proliferation in the mammary gland and the significance of an increased cell proliferation/apoptosis ratio deserve further consideration.	Mainly Positive	Low to medium	↑
Line of Evidence 1: Changes in number of mammary (terminal end) buds volume fraction of (alveolar) buds, and/or (atypical) intraductal epithelial hyperplasia/proliferation *Comment*: Increase in TEBs at one low dose only; small changes (Ayyanan et al., 2011); No dose-response relationship (Acevedo et al., 2013, Vandenberg et al., 2013)	Positive	Low to High	↑↑
Overall conclusion: The EFSA opinion of 2010 noted potential proliferative effects of fetal or perinatal exposure to BPA. Since 2010 additional studies including a study in non-human primates **(**Ayyanan et al., 2011, Tharp, 2012, Vandenberg, 2013, Acevedo, 2013, U.S. FDA/NCTR, 2013) have also suggested that BPA can have proliferative effects on mammary tissues and strengthen the evidence for an effect of BPA on mammary gland proliferation in animals exposed during pre- and post-natal development. **~~Overall likelihood~~**			**Likely** (for mammary gland proliferation)

WOE: 乳腺細胞増殖の例
（証拠としての長所及び短所は省略）

Q2: Does BPA induce proliferative changes in the mammary gland of animals exposed during pre- and/or post-natal (during lactation) development or up to PND 90 (gavage)?	Answer to the question by the study authors (Positive, Negative or Uncertain)	Reliability of evidence (Low, Medium or High)	Influence on Likelihood (see Table 28)
Starting point based on previous assessments (EFSA, 2006, 2010): Based on the reviewed studies the implications of cell proliferation in the mammary gland and the significance of an increased cell proliferation/apoptosis ratio deserve further consideration.	Mainly Positive	Low to medium	↑
Line of Evidence 1: Changes in number of mammary (terminal end) buds volume fraction of (alveolar) buds, and/or (atypical) intraductal epithelial hyperplasia/proliferation *Comment*: Increase in TEBs at one low dose only; small changes (Ayyanan et al., 2011); No dose-response relationship (Acevedo et al., 2013, Vandenberg et al., 2013)	Positive	Low to High	↑↑
Overall conclusion: The EFSA opinion of 2010 noted potential proliferative effects of fetal or perinatal exposure to BPA. Since 2010 additional studies including a study in non-human primates **(**Ayyanan et al., 2011, Tharp, 2012, Vandenberg, 2013, Acevedo, 2013, U.S. FDA/NCTR, 2013) have also suggested that BPA can have proliferative effects on mammary tissues and strengthen the evidence for an effect of BPA on mammary gland proliferation in animals exposed during pre- and post-natal development. **総合的な可能性**			**Likely** (乳腺細胞増殖に関して)

The likelihood assessed by the WOE approach refers to hazard identification, i.e. to the likelihood that BPA has the *inherent capacity* to cause the effect under consideration.

It does not refer to the likelihood of individuals suffering from the effect, which also depends on the dose-response relationship for the effect (hazard characterisation) and the individuals' intake of BPA (considered in exposure assessment).

WOEアプローチで評価された可能性は、危害要因の特定に関連する、すなわち、検討中の影響を引き起こす力をBPAが本質的にもっている可能性を示す.

その可能性は、個人がその影響を患う可能性を示すものではない。個人がその影響を受ける可能性は、その影響の用量反応関係(危害要因の判定)、および各個人が摂取したBPAの量(暴露評価で検討される)にも依存する.

WoE evaluation of genotoxicity, carcinogenicity and effects on cell proliferation in humans and animals

Overall conclusion on BPA GENOTOXICITY	
In vivo genotoxicity studies – via non-thresholded mechanism:	**Unlikely**
In vivo genotoxicity studies - via thresholded mechanism:	**As likely as not**
Overall conclusion on BPA CARCINOGENICITY	
In humans	**Insufficient data for WoE approach**
in animals when exposed during their adult life (post-pubertal) only:	**Unlikely to as like as not**
in animals exposed during pre- and post-natal (during lactation) development:	**Unlikely to as like as not**
Overall conclusion on proliferative changes of BPA induced CELL PROLIFERATION	
in animals when exposed postnatally/ during their adult life:	**As likely as not (for mammary gland proliferation)**
Proliferative changes/ developmental advancement in the mammary gland of animals exposed during pre- and/or post-natal (during lactation) development or up to PND 90 The EFSA opinion of 2010 noted potential proliferative effects of fetal or perinatal exposure to BPA. Since 2010 additional studies (Ayyanan et al., 2011, Tharp, 2012, Vandenberg, 2013, Acevedo, 2013, U.S. FDA/NCTR, 2013) strengthen the evidence for an effect of BPA on mammary gland proliferation in animals	**Likely (for mammary gland proliferation)**

ヒト及び動物における、遺伝毒性、発がん性及び細胞増殖への影響のWOE評価

Overall conclusion on BPA GENOTOXICITY	
In vivo genotoxicity studies – via non-thresholded mechanism:	**Unlikely**
In vivo genotoxicity studies - via thresholded mechanism:	**As likely as not**
Overall conclusion on BPA CARCINOGENICITY	
In humans	**Insufficient data for WOE approach**
in animals when exposed during their adult life (post-pubertal) only:	**Unlikely to as like as not**
in animals exposed during pre- and post-natal (during lactation) development:	**Unlikely to as like as not**
Overall conclusion on proliferative changes of BPA induced CELL PROLIFERATION	
in animals when exposed postnatally/ during their adult life:	**As likely as not (for mammary gland proliferation)**
Proliferative changes/ developmental advancement in the mammary gland of animals exposed during pre- and/or post-natal (during lactation) development or up to PND 90 The EFSA opinion of 2010 noted potential proliferative effects of fetal or perinatal exposure to BPA. Since 2010 additional studies (Ayyanan et al., 2011, Tharp, 2012, Vandenberg, 2013, Acevedo, 2013, U.S. FDA/NCTR, 2013) strengthen the evidence for an effect of BPA on mammary gland proliferation in animals exposed during pre- and post-natal development.	**Likely (for mammary gland proliferation)**

WoE evaluation of neurotoxic effects of BPA in humans and animals

efsa European Food Safety Authority

Human studies	
Overall Likelihood of neurodevelopmental effects of BPA in humans: There are indications from prospective studies that prenatal BPA exposure (BPA exposure during pregnancy) may be associated with child behaviour in a sex-dependent manner. However, the associations were not consistent across the studies. It cannot be ruled out that the results are confounded by diet or concurrent exposure factors. The associations do not provide sufficient evidence to infer a causal link between BPA exposure during pregnancy and neurodevelopmental effects in humans. Potential effects are considered to be as likely as not.	**As likely as not**
Overall Likelihood of neurological/behavioural effects of BPA in humans: There are indications from one prospective study that childhood BPA exposure may be associated with behavioural problems in both girls and boys. It cannot be ruled out that the results are confounded by diet or concurrent exposure factors. The associations do not provide sufficient evidence to infer a causal link between childhood BPA exposure and neurological effects/behavior in humans. Potential effects are considered to be as likely as not.	**As likely as not**
Animal studies	
Overall Likelihood on Anxiety-like behaviour in animals after pre- and/or postnatal exposure to BPA: Several studies report on increased anxiety-like behaviour in rodents after exposure to BPA. Due to the limitation in study design and statistics, and the inconsistency in the reported results, potential effects are considered to be as likely as not.	**As likely as not**
Overall Likelihood on Learning and memory in animals after pre- and/or postnatal exposure to BPA: The effects of BPA on learning and memory abilities of laboratory rodents are no fully consistent, as both positive and negative effects are reported in different papers. The papers have methodological shortcomings, such as underpowered sample size, lack of consideration of the litter effect, or not properly controlled variability of exposure through diet, and inadequate statistics. Potential effects are considered to be as likely as not.	**As likely as not**
Overall Likelihood on Social behaviour in animals after pre- and/or postnatal exposure to BPA: Several new studies evaluating the effects of BPA on social behaviour end points have some methodological shortcomings (litter effect not properly addressed, potential variability of exposure not controlled for) although the behavioural analysis is performed in a scientifically-valid way. However, due to the shortcomings potential effects are considered to be as likely as not.	**As likely as not**
Overall Likelihood on Sensory-motor function in animals after pre- and/or postnatal exposure to BPA: The three studies considered reported some positive effects of BPA on sensory-motor function. The studies present methodological shortcomings, which includes a small sample size and the use of a single administration. Due to the shortcomings, potential effects are considered to be as likely as not.	**As likely as not**

ヒト及び動物におけるBPAの神経行動学的影響のWOE評価

efsa European Food Safety Authority

Human studies	
Overall Likelihood of neurodevelopmental effects of BPA in humans: There are indications from prospective studies that prenatal BPA exposure (BPA exposure during pregnancy) may be associated with child behaviour in a sex-dependent manner. However, the associations were not consistent across the studies. It cannot be ruled out that the results are confounded by diet or concurrent exposure factors. The associations do not provide sufficient evidence to infer a causal link between BPA exposure during pregnancy and neurodevelopmental effects in humans. Potential effects are considered to be as likely as not.	**As likely as not**
Overall Likelihood of neurological/behavioural effects of BPA in humans: There are indications from one prospective study that childhood BPA exposure may be associated with behavioural problems in both girls and boys. It cannot be ruled out that the results are confounded by diet or concurrent exposure factors. The associations do not provide sufficient evidence to infer a causal link between childhood BPA exposure and neurological effects/behavior in humans. Potential effects are considered to be as likely as not.	**As likely as not**
Animal studies	
Overall Likelihood on Anxiety-like behaviour in animals after pre- and/or postnatal exposure to BPA: Several studies report on increased anxiety-like behaviour in rodents after exposure to BPA. Due to the limitation in study design and statistics, and the inconsistency in the reported results, potential effects are considered to be as likely as not.	**As likely as not**
Overall Likelihood on Learning and memory in animals after pre- and/or postnatal exposure to BPA: The effects of BPA on learning and memory abilities of laboratory rodents are no fully consistent, as both positive and negative effects are reported in different papers. The papers have methodological shortcomings, such as underpowered sample size, lack of consideration of the litter effect, or not properly controlled variability of exposure through diet, and inadequate statistics. Potential effects are considered to be as likely as not.	**As likely as not**
Overall Likelihood on Social behaviour in animals after pre- and/or postnatal exposure to BPA: Several new studies evaluating the effects of BPA on social behaviour end points have some methodological shortcomings (litter effect not properly addressed, potential variability of exposure not controlled for) although the behavioural analysis is performed in a scientifically-valid way. However, due to the shortcomings potential effects are considered to be as likely as not.	**As likely as not**
Overall Likelihood on Sensory-motor function in animals after pre- and/or postnatal exposure to BPA: The three studies considered reported some positive effects of BPA on sensory-motor function. The studies present methodological shortcomings, which includes a small sample size and the use of a single administration. Due to the shortcomings, potential effects are considered to be as likely as not.	**As likely as not**

WoE evaluation of reproductive and developmental effects of BPA in humans and animals

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Human studies	
Overall Likelihood of reproductive effects of BPA in humans: An association between BPA and embryo quality and implantation success during IVF, semen quality, sex hormones or age of menarche in humans is considered unlikely	**Unlikely**
Overall Likelihood of gestational /birth outcomes of BPA in humans: There are indications from prospective studies that BPA exposure during pregnancy may be associated with effects on fetal growth, and weak indications that BPA exposure during pregnancy may be associated with maternal and infant thyroid function. However, it cannot be ruled out that the results are confounded by diet or concurrent exposure factors. For fetal growth, two studies showed reduced fetal growth, while one study reported increased fetal growth with increasing maternal BPA exposure. The associations do not provide sufficient evidence to infer a causal link between BPA exposure and reproductive effects in humans. Potential effects are considered to be as likely as not.	**As likely as not**
Animal studies	
Overall Likelihood for reproductive and developmental effects in animals when exposed during their adult life (post-pubertal) only at doses ≤ HED of 3.6 mg/kg bw per day: As more studies emerge with doses ≤3.6 mg BPA/kg bw per day HED, there are increasing indications of some negative effects of adult exposure to BPA on gonadal or reproductive tract physiology. Very few studies have assessed the effects of long term exposure of adults to such doses of BPA (human scenario) on the reproductive gold standard – fertility and reproductive ageing. Since only single studies on ovary and prostate gland fit the methodological criteria used in this opinion, no conclusion can be drawn on BPA-related effects on these organs. Taken together the studies assessed here suggest that BPA at an HED of ≤3.6 mg/kg bw per day may have adverse effects on testis function, especially various measures of spermatogenesis. There is much less evidence to support a conclusion that BPA will significantly impair testis morphology or reproductive endocrinology, especially in the longer term. **Note: Alteration of reproductive capacity are likely at high dose above an HED of 3.6 mg/kg bw per day**	**As likely as not**
Overall Likelihood for reproductive and developmental effects in animals when exposed during development (prenatally and pre-pubertally) ≤ HED of 3.6 mg/kg bw per day: Taken overall, there are some data suggesting negative effects of doses of BPA ≤ an HED of 3.6 mg/kg bw per day on reproductive development in animals. However, the lack of agreement between studies results in a high degree of uncertainty. The most consistent findings are generally of small magnitude (e.g. reduced male AGD) and often not	**As likely as not**

ヒト及び動物におけるBPAの生殖及び発生影響のWOE評価

efsa

Human studies	
Overall Likelihood of reproductive effects of BPA in humans: An association between BPA and embryo quality and implantation success during IVF, semen quality, sex hormones or age of menarche in humans is considered unlikely	**Unlikely**
Overall Likelihood of gestational /birth outcomes of BPA in humans: There are indications from prospective studies that BPA exposure during pregnancy may be associated with effects on fetal growth, and weak indications that BPA exposure during pregnancy may be associated with maternal and infant thyroid function. However, it cannot be ruled out that the results are confounded by diet or concurrent exposure factors. For fetal growth, two studies showed reduced fetal growth, while one study reported increased fetal growth with increasing maternal BPA exposure. The associations do not provide sufficient evidence to infer a causal link between BPA exposure and reproductive effects in humans. Potential effects are considered to be as likely as not.	**As likely as not**
Animal studies	
Overall Likelihood for reproductive and developmental effects in animals when exposed during their adult life (post-pubertal) only at doses ≤ HED of 3.6 mg/kg bw per day: As more studies emerge with doses ≤3.6 mg BPA/kg bw per day HED, there are increasing indications of some negative effects of adult exposure to BPA on gonadal or reproductive tract physiology. Very few studies have assessed the effects of long term exposure of adults to such doses of BPA (human scenario) on the reproductive gold standard – fertility and reproductive ageing. Since only single studies on ovary and prostate gland fit the methodological criteria used in this opinion, no conclusion can be drawn on BPA-related effects on these organs. Taken together the studies assessed here suggest that BPA at an HED of ≤3.6 mg/kg bw per day may have adverse effects on testis function, especially various measures of spermatogenesis. There is much less evidence to support a conclusion that BPA will significantly impair testis morphology or reproductive endocrinology, especially in the longer term. **Note: Alteration of reproductive capacity are likely at high dose above an HED of 3.6 mg/kg bw per day**	**As likely as not**
Overall Likelihood for reproductive and developmental effects in animals when exposed during development (prenatally and pre-pubertally) ≤ HED of 3.6 mg/kg bw per day: Taken overall, there are some data suggesting negative effects of doses of BPA ≤ an HED of 3.6 mg/kg bw per day on reproductive development in animals. However, the lack of agreement between studies results in a high degree of uncertainty. The most consistent findings are generally of small magnitude (e.g. reduced male AGD) and often not accompanied by associated changes (e.g. reduced male AGD expected to be associated with reduced testosterone). Given difficulties in determining whether molecular changes are causal or due to adaptation or morphological changes, the weight given to studies presenting molecular findings without accompanying morphological data is low. The single non-human primate study included was hampered by inadequate numbers of animals per group. **Note: Alteration of reproductive development are likely at high dose above an HED of 3.6 mg/kg bw per day**	**As likely as not**

WoE evaluation of metabolic effects of BPA in humans and animals

Human studies	
Overall conclusion on likelihood of associations between BPA and obesity in humans There are indications from a prospective study that prenatal BPA exposure (maternal urinary BPA concentrations) may be associated with reduced body mass in girls, while cross-sectional studies indicate associations between childhood BPA exposure and obesity. It cannot be ruled out that the results are confounded by diet or concurrent exposure factors. The associations do not provide sufficient evidence to infer a causal link between BPA exposure and obesity in humans. No firm conclusions can be drawn on the likelihood.	**As likely as not**
Overall conclusion on likelihood of associations between BPA and hormonal effects in humans There are indications from one prospective study that maternal BPA exposure may be associated with adipokine expression in 9 year old children, but it cannot be ruled out that the result is confounded by diet or concurrent exposure factors. The association does not provide sufficient evidence to infer a causal link between BPA exposure and hormonal effects in humans. No firm conclusions can be drawn on the likelihood.	**As likely as not**
Overall conclusion on likelihood of associations between BPA and diabetes effects in humans: The indications that BPA may be associated with diabetes in humans is unlikely.	**Unlikely**
Overall conclusion on likelihood of associations between BPA and metabolic syndrome in humans: The indication that BPA may be associated with metabolic syndrome in humans is unlikely.	**Unlikely**
Animal studies	
The indication that BPA may be associated with renal function in humans is unlikely. **Overall conclusion on likelihood of metabolic effects in animals exposed postnatally** Evidence for associations between BPA exposure and metabolic effects in animals exposed postnatally is inconsistent. There is reasonable evidence for effects on glucose or insulin regulation and/or effects on pancreatic morphology and/or function in shorter term studies, but no evidence that BPA is causing diabetes, insulin resistance and increases in weight (obesogenic) longer-term.	**As likely as not**
Overall conclusion on likelihood of metabolic effects in animals exposed prenatally : Since the initial reports that BPA had potential effects on adiposity, glucose or insulin regulation, lipids and other end-points related to diabetes or metabolic syndrome in animals exposed prenatally, several new studies have been published. There is reasonable evidence for effects on glucose or insulin regulation and/or effects on pancreatic morphology and/or function in shorter term studies, but no evidence that BPA is causing diabetes, insulin resistance and increases in weight (obesogenic) longer-term.	**As likely as not**

ヒト及び動物におけるBPAの代謝への影響のWOE評価

Human studies	
Overall conclusion on likelihood of associations between BPA and obesity in humans There are indications from a prospective study that prenatal BPA exposure (maternal urinary BPA concentrations) may be associated with reduced body mass in girls, while cross-sectional studies indicate associations between childhood BPA exposure and obesity. It cannot be ruled out that the results are confounded by diet or concurrent exposure factors. The associations do not provide sufficient evidence to infer a causal link between BPA exposure and obesity in humans. No firm conclusions can be drawn on the likelihood.	**As likely as not**
Overall conclusion on likelihood of associations between BPA and hormonal effects in humans There are indications from one prospective study that maternal BPA exposure may be associated with adipokine expression in 9 year old children, but it cannot be ruled out that the result is confounded by diet or concurrent exposure factors. The association does not provide sufficient evidence to infer a causal link between BPA exposure and hormonal effects in humans. No firm conclusions can be drawn on the likelihood.	**As likely as not**
Overall conclusion on likelihood of associations between BPA and diabetes effects in humans: The indications that BPA may be associated with diabetes in humans is unlikely.	**Unlikely**
Overall conclusion on likelihood of associations between BPA and metabolic syndrome in humans: The indication that BPA may be associated with metabolic syndrome in humans is unlikely.	**Unlikely**
Overall conclusion on likelihood of associations between BPA and renal effects in humans: The indication that BPA may be associated with renal function in humans is unlikely.	**Unlikely**
Animal studies	
Overall conclusion on likelihood of metabolic effects in animals exposed postnatally Evidence for associations between BPA exposure and metabolic effects in animals exposed postnatally is inconsistent. There is reasonable evidence for effects on glucose or insulin regulation and/or effects on pancreatic morphology and/or function in shorter term studies, but no evidence that BPA is causing diabetes, insulin resistance and increases in weight (obesogenic) longer-term.	**As likely as not**
Overall conclusion on likelihood of metabolic effects in animals exposed prenatally : Since the initial reports that BPA had potential effects on adiposity, glucose or insulin regulation, lipids and other end-points related to diabetes or metabolic syndrome in animals exposed prenatally, several new studies have been published. There is reasonable evidence for effects on glucose or insulin regulation and/or effects on pancreatic morphology and/or function in shorter term studies, but no evidence that BPA is causing diabetes, insulin resistance and increases in weight (obesogenic) longer-term.	**As likely as not**

General Toxicity

- BPA caused significant changes in kidney and liver weight in rats and mice in the multi-generation studies by Tyl et al. in 2002 and 2008.
- In mouse kidney: also nephropathy at the highest dose; in rats: renal tubular degeneration at the highest dose in all female generations.
- Liver weight was increased in rats and mice, the latter species also showing hepatocyte hypertrophy.

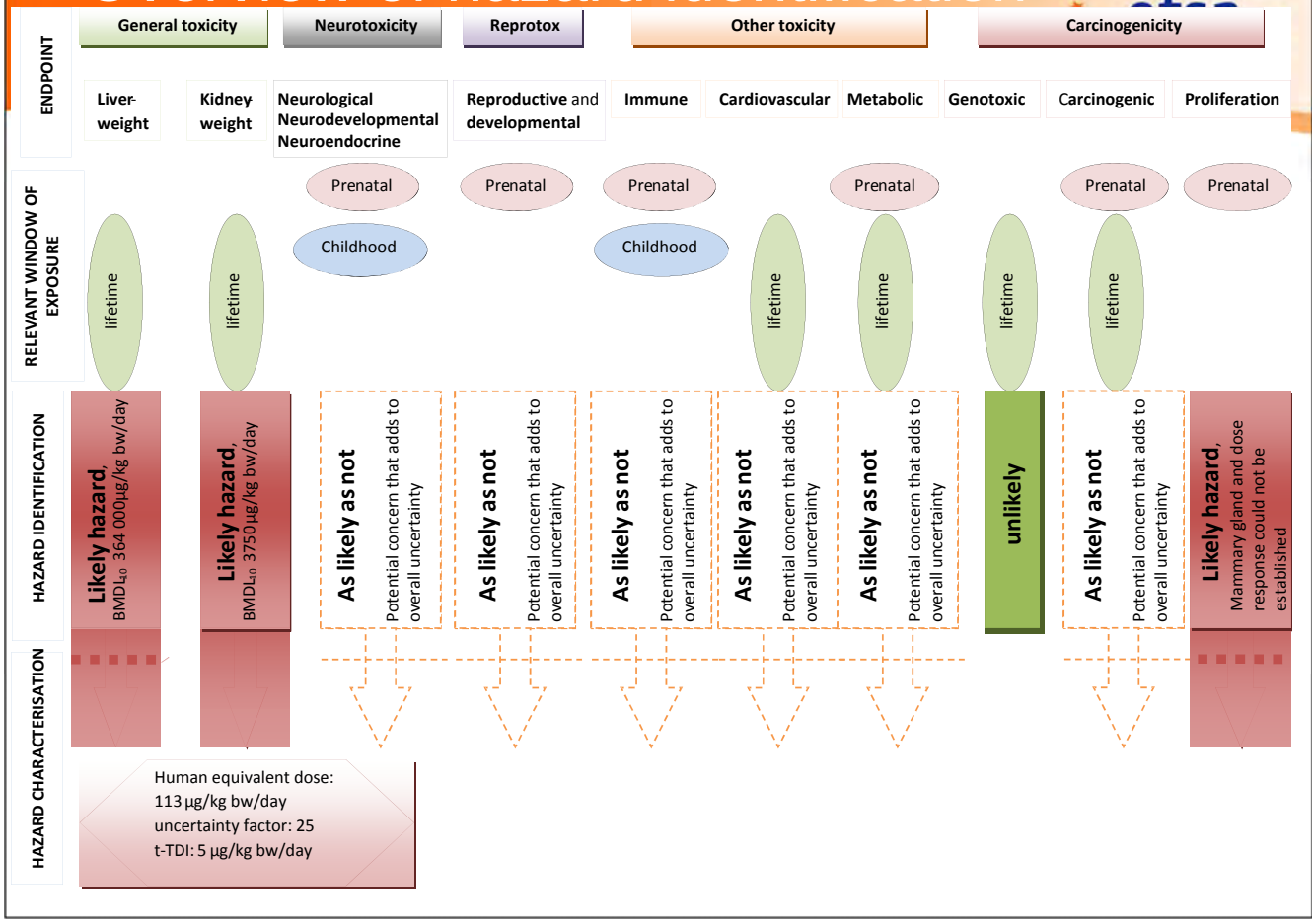
- Altogether, these observations suggest that changes in the kidney and liver are critical endpoints in BPA toxicity, and the endpoint was used for risk characterisation

一般毒性

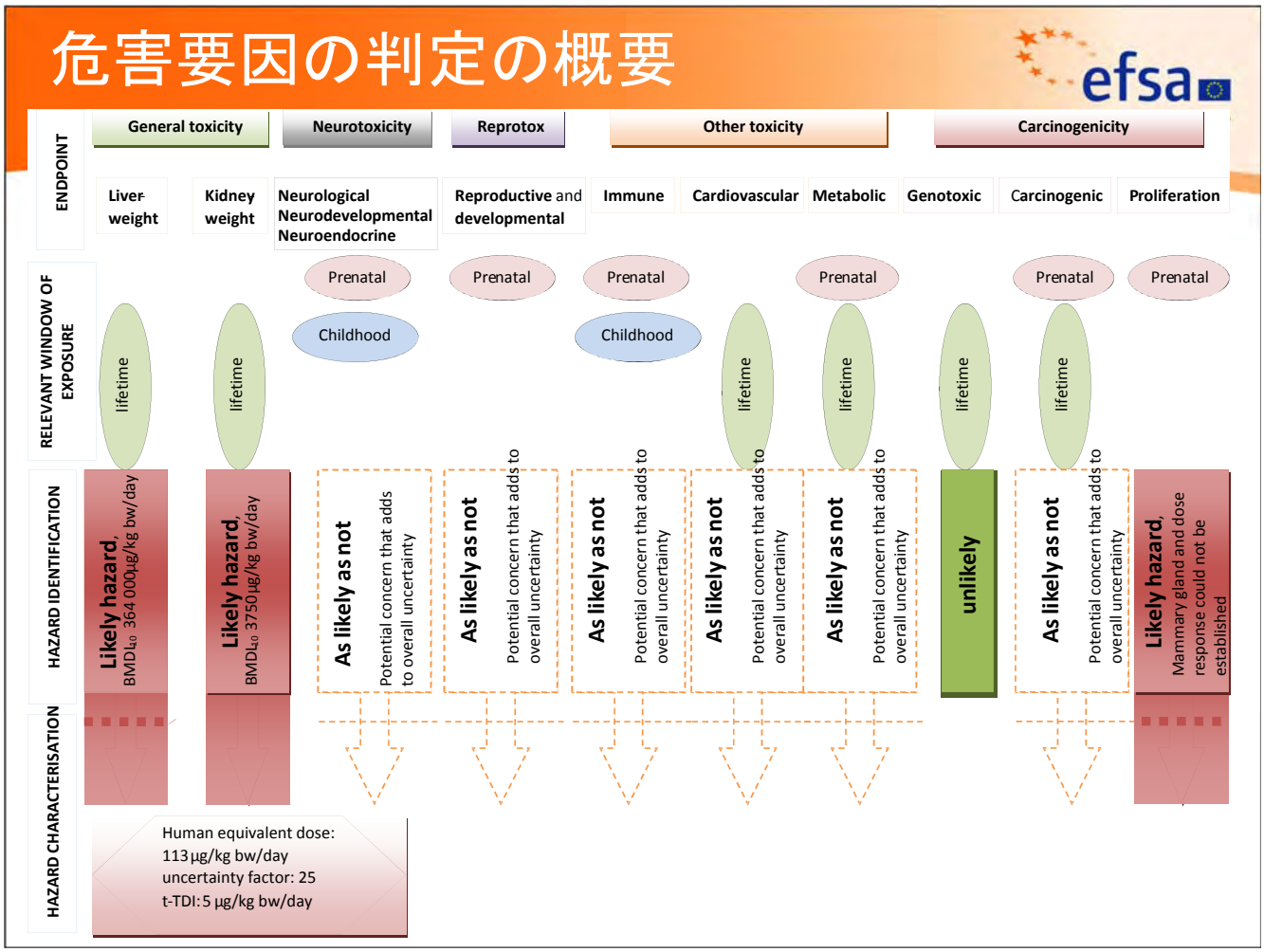
- Tyl らの2002，2008年の多世代試験で、BPAはラットとマウスの腎および肝の重量に有意な変化をもたらした.
- また、BPA の最高用量では、マウスでは腎障害を、ラットでは全世代の雌に尿細管の変性を引き起こした.
- ラット及びマウスで肝重量が増加し、特にマウスでは肝細胞肥大が認められた.

- 以上の結果は、腎および肝における変化は、BPAの毒性の重要なエンドポイントであることを示唆し、それらのエンドポイントを危害要因の判定に用いた。

Overview of hazard identification



危害要因の判定の概要



Hazard characterization

- **"Likely" adverse effects in animals**, i.e. on kidney, liver and mammary gland were brought forward for hazard characterization.
- **Benchmark dose response modelling** was carried out for "likely" effects, considering the most robust sets of data.

危害要因の判定

- 危害要因の判定には、動物に**「現れる可能性のある」**有害影響（すなわち、腎臓、肝臓及び乳腺に対する影響）を用いた。
- **ベンチマークドーズ用量反応モデル**は、もっとも強固なデータセットを考慮して、「現れる可能性のある」影響について適用した。

Hazard characterisation: BMD modelling of Tyl 2008 data in mice

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Dose response relationships for general toxicity of BPA in mice (Tyl et al., 2008)

Study	Mouse generation	Route of administration	Toxic effect	External dose level (ug/kg bw per day)	
				BMDU10	BMDL10
Tyl et al., 2008	F0 females, with sex and F0/F1 as covariate	Oral feed	Increased liver weight	522500	364400
Tyl et al., 2008	F0 males, with sex and F0/F1 as covariate	Oral feed	Centrilobular hepatocyte hypertrophy	35500	3460
Tyl et al., 2008	F0 males, with sex and F0/F1 as covariate	Oral feed	Increased right kidney weight	99220	**3633**
Tyl et al., 2008	F0 males, with sex and F0/F1 as covariate	Oral feed	Increased left kidney weight	120100	**3887**

Although the lowest BMDL10 from the modelling was for hepatocyte hypertrophy, this effect of BPA was regarded as adaptive.
The critical endpoint was considered kidney weight in the mouse, resulting in a **BMDL10 of 3633 µg/kg bw per day and 3887 µg/kg bw per day** for the left and right kidney, respectively.

危害要因の判定: マウスにおけるデータ（Tyl 2008）のBMDモデリング

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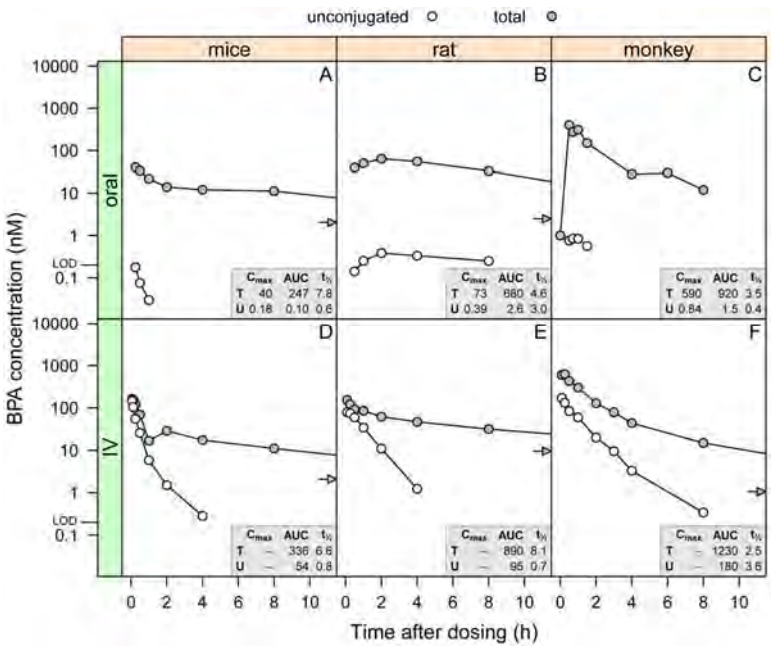
マウスにおけるBPAの一般毒性の用量反応関係 (Tyl et al., 2008)

Study	マウス世代	投与経路	毒性影響	外部投与量レベル (ug/kg bw per day)	
				BMDU10	BMDL10
Tyl et al., 2008	マウス(F0)メス、性別及びF0/F1を共変数とする	経口混餌	肝臓重量の増加	522500	364400
Tyl et al., 2008	マウス(F0)オス、性別及びF0/F1を共変数とする	経口混餌	小葉中心性の肝細胞肥大	35500	3460
Tyl et al., 2008	マウス(F0)オス、性別及びF0/F1を共変数とする	経口混餌	右腎重量の増加	99220	**3633**
Tyl et al., 2008	マウス(F0)オス、性別及びF0/F1を共変数とする	経口混餌	左腎重量の増加	120100	**3887**

当該モデルで得られたBMDL10の最小値は肝細胞肥大だったが、BPAのこの影響は生体適合反応とみなされた。
重要なエンドポイントは、マウスにおける腎重量と考えられ、その結果、**BMDL10はそれぞれ、左腎3633 µg/kg 体重/日、右腎3887 µg/kg 体重/日だった。**

Toxicokinetics

Time course of serum levels of unconjugated and total BPA in adult mice, rats, and rhesus monkeys following oral administration or IV injection of a single dose of 100 µg/kg bw per day of isotope-labelled (deuterated) BPA.



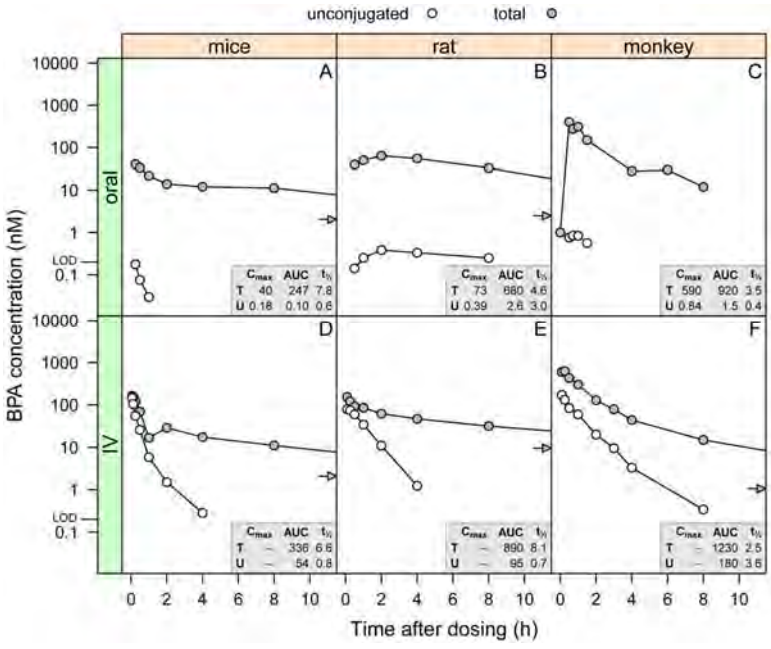
Note the low levels of free-BPA after oral exposure

New study in mice, free BPA below LOD

Uncertainty

トキシコキネティクス

同位体標識（重水素化）BPA100 µg/kg 体重/日単回投与（経口又は静脈内投与）後のマウス、ラット及びアカゲザルの成獣における非抱合型及び総BPAの血清レベルの時間的経過



経口投与後の遊離型BPAのレベルが低いことに注目

マウスにおける新たな試験では、遊離型BPAが検出限界を下回った

不確実性

Hazard characterisation - Oral human equivalent dose (HED)

- **Why deriving an HED?**: to translate the critical dose found in animal studies to the correspondent oral dose for humans
- **Definition of HED:** is the multiples of the BPA dose (D) in an animal species by a specified route and lifestage that a human would require to obtain an equivalent AUC from oral administration
- **Calculation of HED**: the critical dose for the key effect (i.e. BMDL, NOAEL) in animals is multiplied by a factor (i.e. HEDF) that takes into account the quantitative differences in toxicokinetics between the animal species used in the study and humans.
  - HED = BMDL x HEDF
- AUCs are used to calculate Human Equivalent Dose adjustment Factor (HEDF)
  - HEDF = AUCanimal / AUChuman

危害要因の特定 – 経口ヒト等価用量 (HED)

- **何のためにHEDを算出するか:** 動物実験で得られた 重要な投与量を、人に対し相当する経口投与量に変換するために用いる.
- HEDの定義とは:動物で特定の投与経路と特定のライフステージで投与されたBPAのAUCと等量のAUCがヒトで得られるに必要な経口投与用量に係数をかけた数値.
- HEDの計算: 動物試験から得られた主要な影響に関する重要な投与量(すなわちBMDL, NOAEL)に、試験に用いられた動物種とヒトの間のトキシコキネティクスにおける定量的違いを考慮した係数(すなわちHEDF)を乗じる.
  - HED = BMDL x HEDF
- ヒト等価用量調整係数(HEDF)を計算するためにAUCを用いる.
  - HEDF = AUCanimal / AUChuman

Human-Equivalent Dosimetric Factors (HEDF) for BPA

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Determination of Human-Equivalent Dosimetric Factors (HEDF) for BPA in human adults

Species-Route	AUC-Adult (nmol × h × l–1)	HEDF-Adult	DAF- Adult bw¾ Scaling
Mouse-oral Mouse – IV injection	0.1 54	0.03 (= 0.1/3.6) 15 (= 54 /3.6)	0.14 = (0.025/70)1/4
Rat-oral Rat – IV injection	2.6 95	0.72 (= 2.6/3.6) 26 (= 95 /3.6)	0.24 = (0.25/70)1/4
Monkey-oral Monkey – IV injection	1.5 180	0.42 (= 1.5/3.6) 50 (=180/3.6)	0.55# = (6.6/70)1/4
Human-oral PBPK-simulation; Yang et al. (2013)	3.6 (reference value)	–	–

Determination of Human-Equivalent Dosimetric Factors (HEDF*) for BPA in human infants

Species-Route	AUC-Neonate (nmol × h × l–1)	HEDF-Neonate
Mouse-oral Mouse – SC injection	26 26	8.7 (= 26/3) 8.7 (= 26/3)
Rat-oral Rat – SC injection	56 930	19 (= 56/3) 310 (= 930/3)
Monkey-oral Monkey – IV injection	5.7 190	1.9 (= 5.7/3) 63 (=190/3)
Human-oral PBPK-simulation (Yang et al. (2013)	3.0 (reference value)	–

BPAのヒト等価用量調整係数(HEDF)

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ヒト成人におけるHEDFの決定

動物種-経路	AUC-成人 (nmol × h × l–1)	HEDF-成人	DAF- 成人 bw¾ Scaling
マウス－経口 マウス– 静脈内	0.1 54	0.03 (= 0.1/3.6) 15 (= 54 /3.6)	0.14 = (0.025/70)1/4
ラット経口 ラット– 静脈内	2.6 95	0.72 (= 2.6/3.6) 26 (= 95 /3.6)	0.24 = (0.25/70)1/4
サル-経口 サル – 静脈内	1.5 180	0.42 (= 1.5/3.6) 50 (=180/3.6)	0.55# = (6.6/70)1/4
ヒト-経口 PBPKシミュレーション; Yang et al. (2013)	3.6 (reference value)	–	–

ヒト乳児におけるHEDFの決定

動物種-経路	AUC-新生児 (nmol × h × l–1)	HEDF-新生児
マウス－経口 マウス– 静脈内	26 26	8.7 (= 26/3) 8.7 (= 26/3)
ラット経口 ラット– 静脈内	56 930	19 (= 56/3) 310 (= 930/3)
サル-経口 サル – 静脈内	5.7 190	1.9 (= 5.7/3) 63 (=190/3)
ヒト-経口 PBPKシミュレーション; Yang et al. (2013)	3.0 (reference value)	–

Hazard characterisation – from BMDL to t-TDI

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Outcome of the BMD analysis for effects of BPA on kidney weight in mice and conversion to HED (Tyl et al., 2008)

Species (generation)	Route of administration	Toxic effect	External dose (µg/kg bw per day)		HED (µg/kg bw per day)
			$BMDL_{10}$	$BMDU_{10}$	
Mice (F0) males, with sex and F0/F1 as covariate	Oral feed	Increased left kidney weight	3 633	99 220	109
Mice (F0) males, with sex and F0/F1 as covariate	Oral feed	Increased right kidney weight	3 887	120 100	117

3633 x 0.03 (HEDF oral mice) = 109

3887 x 0.03 (HEDF oral mice) = 117

Using data on interspecies differences in toxicokinetics, in a conservative way this **$BMDL_{10}$ is converted to an oral human equivalent dose (HED) of 113 µg/kg bw per day.**

An uncertainty factor of 25 was then applied to the mean HED of 113 µg/kg bw per day to derive a t-TDI of 5 µg/kg bw per day.

危害要因の判定 –BMDLから暫定TDIまで

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マウスの腎臓重量へのBPAの影響についてのベンチマークドーズ分析結果及びヒト等価用量への換算 (Tyl et al., 2008)

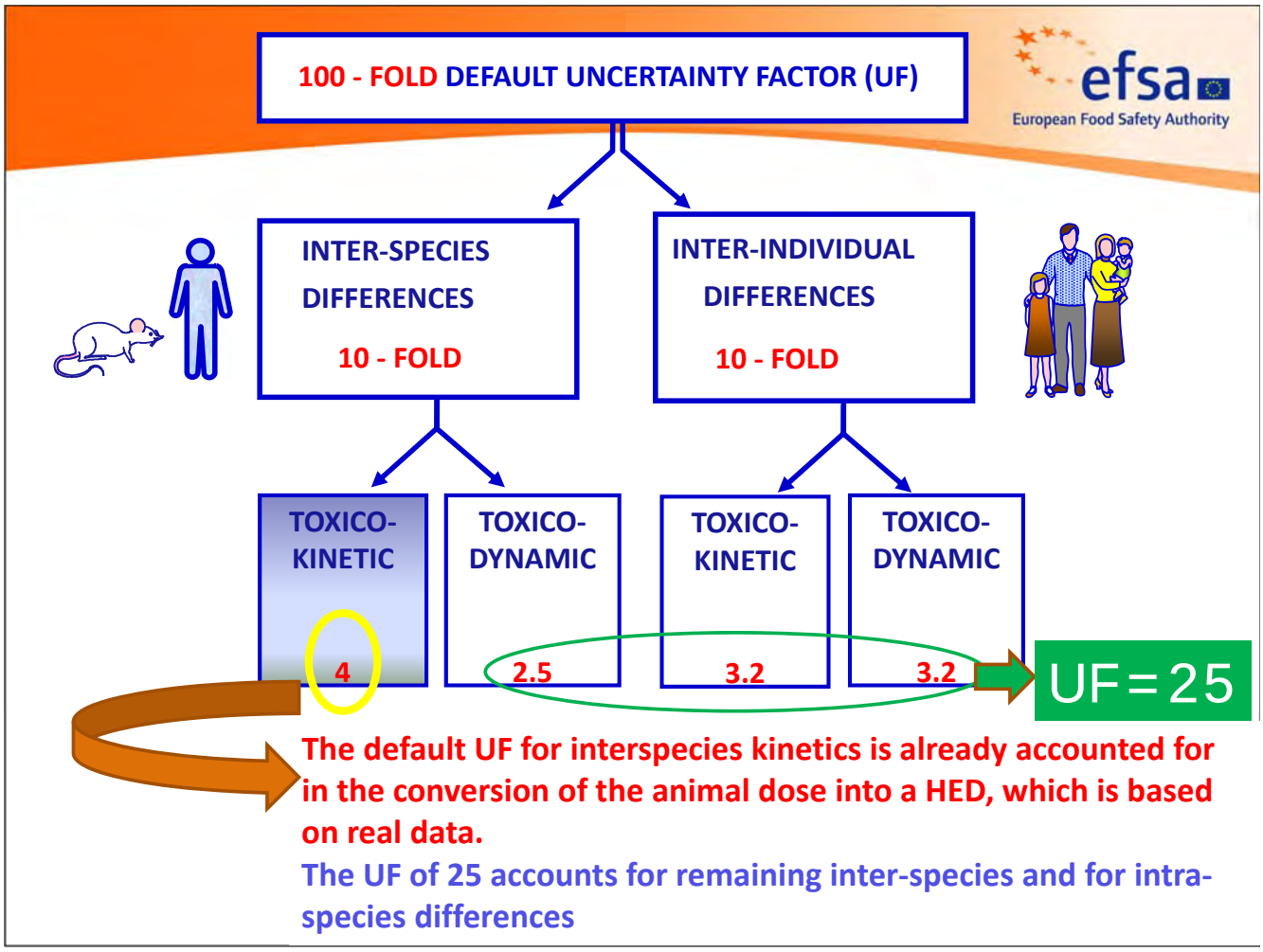
動物種（世代）	投与経路	毒性学的影響	外部投与量 (µg/kg bw/day)		ヒト等価用量 (µg/kg bw/day)
			$BMDL_{10}$	$BMDU_{10}$	
マウス(F0)オス、性別及びF0/F1を共変数とする	経口混餌	左腎重量の増加	3 633	99 220	109
マウス(F0)オス、性別及びF0/F1を共変数とする	経口混餌	右腎重量の増加	3 887	120 100	117

3633 x 0.03 (HEDF oral mice) = 109

3887 x 0.03 (HEDF oral mice) = 117

トキシコキネティクスにおける種差に関するデータを用いて、慎重な(conservative)方法で、当該**$BMDL_{10}$ は経口ヒト等価用量（HED) 113 µg/kg bw per dayに換算された。**

不確実係数25を平均ヒト等価用量（113 µg/kg bw per day）に適用し、暫定TDI（5 µg/kg bw per day）を算出した.


100 - FOLD DEFAULT UNCERTAINTY FACTOR (UF)
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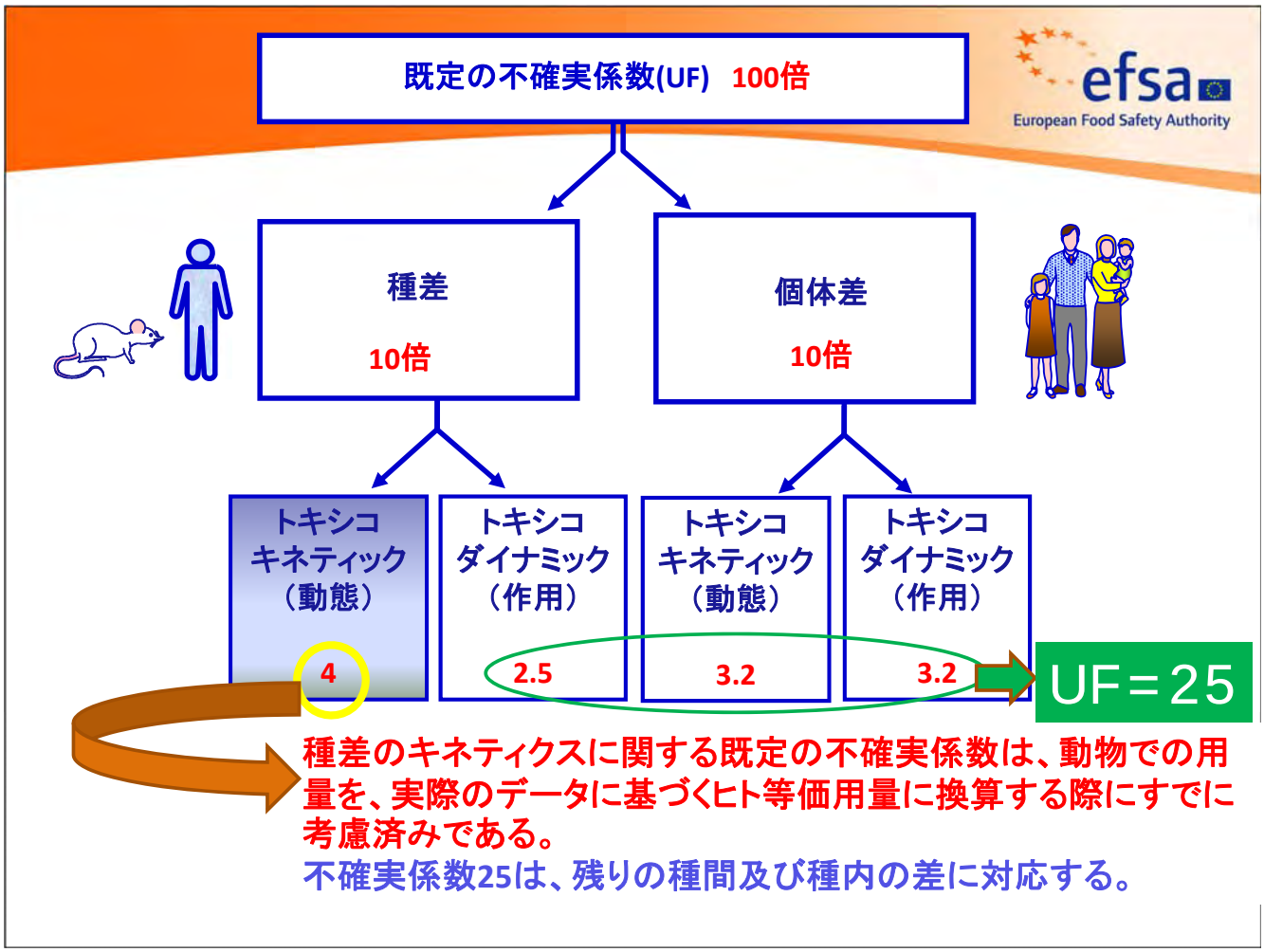
INTER-SPECIES DIFFERENCES
10 - FOLD
INTER-INDIVIDUAL DIFFERENCES
10 - FOLD
TOXICO-KINETIC
TOXICO-DYNAMIC
TOXICO-KINETIC
TOXICO-DYNAMIC
4
2.5
3.2
3.2
UF = 25
The default UF for interspecies kinetics is already accounted for in the conversion of the animal dose into a HED, which is based on real data.
The UF of 25 accounts for remaining inter-species and for intra-species differences


既定の不確実係数(UF) 100倍
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種差
10倍
個体差
10倍
トキシコキネティック（動態）
トキシコダイナミック（作用）
トキシコキネティック（動態）
トキシコダイナミック（作用）
4
2.5
3.2
3.2
UF = 25
種差のキネティクスに関する既定の不確実係数は、動物での用量を、実際のデータに基づくヒト等価用量に換算する際にすでに考慮済みである。
不確実係数25は、残りの種間及び種内の差に対応する。

Temporary TDI (t-TDI) for BPA

- A **t-TDI** of **5 µg/kg bw/day** (rounded from 4.5 µg/kg bw/day) is derived for an external oral exposure to BPA in humans, based on the HED of 113 µg/kg bw per day for increased kidney weight in the mouse, by applying an uncertainty factor of 25.

- **This temporary value reflects the current uncertainties** surrounding effects of BPA on the mammary gland and other potential "less likely" health hazards (neurobehavioural, metabolic, reproductive and immune effects).

BPAの暫定TDI

- **暫定TDI 5 µg/kg bw/day** (4.5 µg/kg bw/dayから四捨五入) は、マウスにおける腎臓重量増加のヒト等価用量(113 µg/kg bw per day)に不確実係数25を適用し、ヒトにおける外部経口暴露量として算出された。

- **当該暫定値は、**乳腺へのBPAの影響に関する**現在の不確実性及びその他の「より可能性の低い」健康危害要因(神経行動学的、代謝、生殖及び免疫への影響)を反映している。**

Dermal exposure expressed as equivalent oral dose based on PBPK modelling

Dermal dose (D_D) expressed as equivalent oral dose (D'_D) for **average** exposure

Population group		D_O	D_D	AUC_O	AUC_D	D'_D	D'_D/D_D
Exposure assessment	PBPK modelling	ng/kg bw/d		pmol × h × l–1		ng/kg bw/d	
Adult males 18 – 45 years	Adult male	126	59	1.37	0.86	**79**	1.34
Teenagers	Adult male	159	94	1.73	1.37	**126**	1.34
Other children 3 – 10 years	Children 1.5 – 4.5 years	290	69	2.60	0.53	**59**	0.87

Dermal dose (D_D) expressed as equivalent oral dose (D'_D) for **High** exposure

Population group		D_O	D_D	AUC_O	AUC_D	D'_D	D'_D/D_D
Exposure assessment	PBPK modelling	ng/kg bw/d		pmol × h × l–1		ng/kg bw/d	
Adult males 18 – 45 years	Adult male	335	542	3.65	7.90	**725**	1.34
Teenagers	Adult male	381	863	4.16	12.58	**1152**	1.34
Other children 3 – 10 years	Children 1.5 – 4.5 years	813	550	7.28	4.21	**470**	0.85

PBPKモデリングに基づく等価経口用量として示される経皮暴露量

平均的な暴露について、等価経口用量(D'_D)として示される経皮用量(D_D)

評価対象集団		経口暴露量	経皮暴露量	AUC_O（経口）	AUC_D（経皮）	D'_D	D'_D/D_D
暴露評価	PBPKモデリング	ng/kg bw/d		pmol × h × l–1		ng/kg bw/d	
成人男性 18 – 45歳	成人男性	126	59	1.37	0.86	**79**	1.34
ティーンエイジャー	成人男性	159	94	1.73	1.37	**126**	1.34
その他の小児 3 – 10歳	小児 1.5 – 4.5歳	290	69	2.60	0.53	**59**	0.87

高暴露について、等価経口用量(D'_D)として示される経皮用量(D_D)

評価対象集団		経口暴露量	経皮暴露量	AUC_O（経口）	AUC_D（経皮）	D'_D	D'_D/D_D
暴露評価	PBPKモデリング	ng/kg bw/d		pmol × h × l–1		ng/kg bw/d	
成人男性 18 – 45歳	成人男性	335	542	3.65	7.90	**725**	1.34
ティーンエイジャー	成人男性	381	863	4.16	12.58	**1152**	1.34
その他の小児 3 – 10歳	小児 1.5 – 4.5歳	813	550	7.28	4.21	**470**	0.85

Risk characterisation/1

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Summary table on average and high ingestion (oral) and dermal (external and dermal equivalent oral dose) exposure to BPA in the general population (ng/kg bw per day)

Age group	Ingestion		Dermal		Dermal (Equivalent oral dose by PBPK modelling)	
	Average	High	Average	High	Average	High
Infants 1-5 d (breastfed)	225	435	0	0	-	-
Infants 6 d- 3 mo (breastfed)	189	361	4.8	9.4	-	-
Infants 4-6 months (breastfed)	168	319	4.8	9.4	-	-
Infants 0-6 months (formula fed)	39	96	4.8	9.4	-	-
Infants 6-12 months	384	873	4.8	9.4	-	-
Toddlers 1-3 yrs	382	870	2.8	5.5	-	-
Children 3-10 yrs	293	818	71	554	59	470
Teenagers 10-18 yrs	161	384	96	868	126	1152
Women 18-45 yrs	132	389	61	546	79	725
Men 18-45 yrs	127	336	61	546	79	725
Adults 45-65 yrs	127	342	61	546	79	725
Elderly and very elderly <65 yrs	117	376	61	546	79	725

Aggregated exposure

リスクの判定/1

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一般集団におけるBPAに対する平均的及び高用量の摂取（経口）及び経皮（外部及び経皮等価経口用量）暴露量(ng/kg bw per day)の総括表

年齢グループ	摂取		経皮		経皮 (PBPKモデリングによる等価経口用量)	
	平均	高用量	平均	高用量	平均	高用量
生後1-5 日 (母乳)	225	435	0	0	-	-
生後6 日～ 3ヶ月 (母乳)	189	361	4.8	9.4	-	-
生後4-6ヶ月 (母乳)	168	319	4.8	9.4	-	-
生後 0-6ヶ月 (調整乳)	39	96	4.8	9.4	-	-
生後6-12ヶ月	384	873	4.8	9.4	-	-
幼児1-3 歳	382	870	2.8	5.5	-	-
小児 3-10歳	293	818	71	554	59	470
ティーンエイジャー10-18 歳	161	384	96	868	126#	1152m#
女性 18-45歳	132	389	61	546	79*	725*
男性18-45歳	127	336	61	546	79	725
成人 45-65歳	127	342	61	546	79*	725*
高齢者及び後期高齢者 65歳以上	117	376	61	546	79*	725*

暴露量の合計

Risk characterisation/2

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Aggregated oral and dermal exposure for the population group other children 3 – 10 years and teenagers

	Other children 3 – 10 years (ng/kg bw per day)		Teenagers (ng/kg bw per day)	
Route of exposure	Oral average (o)	Oral high (0)	Oral average (o)	Oral high (o)
Dermal average (d)	59 (d) 293 (o) 352	59 (d) 818 (O) 877	126 (d) 161(o) 287	126 (d) 384(O) 510
Dermal high (D)	470 (D) 293 (o) 763	**470 (D) 818 (O) 1 288**	1152 (D) 161(o) 1 313	**1152 (D) 384(O) 1 536**

Dermal exposure contributes more than oral

The aggregated HIGH exposure for other children (1 288 ng/kg bw per day) and teenagers (1 536 ng/kg bw per day) is approximately 3-4 fold below the proposed t- TDI of 5 µg/kg bw per day

リスクの判定/2

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その他の小児（3歳から10歳）及びティーンエイジャーの経口・経皮暴露量の合計

	その他の小児（3歳から10歳） (ng/kg bw per day)		ティーンエイジャー (ng/kg bw per day)	
暴露経路	経口平均 (o)	経口高暴露 (0)	経口平均 (o)	経口高暴露 (o)
経皮平均 (d)	59 (d) 293 (o) 352	59 (d) 818 (o) 877	126 (d) 161(o) 287	126 (d) 384.3(o) 510
経皮高暴露(d)	470 (d) 293 (o) 763	470 (d) 818 (o) 1 288	1152 (d) 161(o) 1 313	**1152 (d) 384.3(o) 1 536**

経皮暴露は、経口暴露より寄与が大きい

その他の小児 (1288 ng/kg bw per day)及びティーンエイジャー(1536 ng/kg bw per day)の暴露量の合計は、提案されている暫定TDI（5 µg/kg bw/day）のおよそ3～4分の1である。

Risk characterization/3

- Aggregated high - oral plus dermal - exposure estimates for all age groups ranged from 1 061 in **adult men** to 1 536 ng/kg bw per day in **teenagers**.
- High oral exposure estimates **for infants** (all age groups**) and toddlers** were up to 873 ng/kg bw per day. For these groups, no dermal exposure was identified / anticipated.
- Even for the most exposed groups in the population, aggregated - oral plus dermal – exposure is well below the t-TDI of 5 µg/kg bw per day.
- The **health concern for BPA is low** at the current level of exposure.
- Same conclusions also apply to the **offspring of mothers exposed during pregnancy and to the elderly**

リスクの判定/3

- 全ての年齢グループにおける高暴露量の合計（経口プラス経皮）推計値は、**成人男性**における1061ng/kg bw per day から**ティーンエイジャー**における1 536 ng/kg bw per dayまでの幅がある。
- **乳児**（すべての年齢グループ）**及び 幼児の経口の高暴露推計量は、最高**873 ng/kg bw per dayであった。これらのグループについては、経皮暴露は特定／予期されていない。
- もっとも高い暴露を受けているグループであっても、暴露量の合計（経口プラス経皮）は、暫定TDI（5 µg/kg bw per day）より十分低い。
- 現状の暴露レベルにおけるBPAの健康影響に関する懸念は低い
- 妊娠中に暴露した母体の子及び高齢者についても、同じ結論が当てはまる。

Thank you

..for your kind attention !!…

..and thanks to the Working Groups on BPA and the CEF Panel for this work

謝辞

御清聴ありがとうございました。

また、BPAのワーキンググループ及びCEFパネルに、本評価についての謝意を示します。