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Draft opinion of bisphenol A (BPA) Exposure and Toxicology

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Outline

- Draft exposure assessment
  - Dietary exposure
  - Non-dietary exposure
- Draft assessment of human health risk
  - Hazard identification
    - Weight of evidence (WoE) approach
    - Toxicokinetics
    - Human equivalent dose (HED) approach
  - Hazard characterisation
  - Risk characterisation

Self mandate of the CEF Panel on BPA

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

- To evaluate the toxicity for humans, incl. vulnerable groups (e.g. pregnant women, infants and children, etc.);
- To assess human exposure (based on occurrence data from public literature or submitted to EFSA) from dietary and non-dietary sources (incl. vulnerable groups), & also account for biomonitoring data;
- To characterize the health risks for the general population and for vulnerable groups

Draft Exposure assessment

Exposure assessment

- To assess average and high chronic exposure to BPA through different sources and routes of exposure in the EU population
- Specific scenarios were developed to cover the exposure patterns in the different age classes and vulnerable groups
- Assessment of acute exposure, exposure in specific disease states or occupational exposure were not included

Dietary exposure

- Based on a total of 2521 samples (screening of scientific literature + EFSA call for data)
- Average exposure:
  - Average concentration + Average consumptions
- High exposure:
  - Average concentration + High consumption

Non-dietary exposure

- The term “non-food sources” summarizes all sources that contribute to exposure via pathways other than the food pathway
  - Thermal paper
  - Cosmetics
  - Dust
  - Indoor air

Exposure to BPA from all sources

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Table 23: Exposure to BPA from all sources in the general population (ng/kg bw/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)		2.6	2.6	2.6	2.6	1.1	1.3	0.2	0.1	0.1	0.1	0.1
Dust (high)		31.0	31.0	31.0	31.0	12.9	4.6	4.6	2.9	2.9	2.9	2.9
Toys (average)		0.3	0.3	0.3	0.3	0.02						
Toys (high)		1.2	1.2	1.2	1.2	0.5						
Dietary exposure from food and beverages (average)	225	135	119	30	375	375	290	159	132	126	126	116
Dietary exposure from food and beverages (high)	495	390	343	80	857	857	813	381	388	335	341	375
Sum of all ingestion sources (average)	**225**	**138**	**122**	**33**	**378**	**376**	**292**	**159**	**132**	**127**	**126**	**116**
Inhalation:												
Air (average)	2.4	2.4	2.4	2.4	2.4	1.4	0.7	1.1	0.7	0.7	0.7	0.7
Air (high)	5.8	5.8	5.8	5.8	5.8	3.4	1.8	2.1	1.3	1.3	1.3	1.3
Sum of all inhalation sources (average)	**2.4**	**2.4**	**2.4**	**2.4**	**2.4**	**1.4**	**0.7**	**1.1**	**0.7**	**0.7**	**0.7**	**0.7**
Dermal:												
Thermal paper (average)							21	28	18	18	18	18
Thermal paper (high)							165	259	163	163	163	163
Cosmetics (average)		2.9	2.9	2.9	2.9	1.7	1.3	1.5	1.2	1.2	1.2	1.2
Cosmetics (high)		5.6	5.6	5.6	5.6	3.3	2.5	2.9	2.4	2.4	2.4	2.4
Sum of all dermal sources (average)		**3**	**3**	**3**	**3**	**2**	**22**	**30**	**19**	**19**	**19**	**19**
Total exposure from all sources (average)	**228**	**143**	**127**	**38**	**383**	**379**	**314**	**190**	**152**	**146**	**145**	**136**
Total exposure (high) calculated as two highest plus sum of the average of all other sources	**501**	**427**	**380**	**117**	**894**	**873**	**981**	**642**	**553**	**500**	**506**	**540**

Draft conclusions – Dietary exposure

- Overall, among the population older than 6 months, infants and toddlers presented the highest estimated average (375 ng/kg bw/day) and high (857 ng/kg bw/day) dietary exposure.

- 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

Draft conclusions – Non-dietary exposure

- For the children above 3 years, teenagers and adults thermal paper is the main non-food source, for both average (21, 28 and 18 ng/kg bw/day) and high (165, 259 and 163 ng/kg bw/day) exposure

- The average values for thermal paper differed by a factor 10 from the respective high values. This is due to highly conservative assumption when assessing high exposure

- Exposure to dust, cosmetics and indoor air was less important

Draft assessment of human health risk

Hazard identification - Weight of evidence (WoE) approach

- For the hazard identification of BPA, the WoE approach was structured in such a way as to facilitate consistent treatment of the evidence and to document this in a tabular format

- The WoE evaluation for each toxicological endpoint was divided into one or several parts addressing different questions considered by the Panel to be relevant for hazard identification of BPA

- Subsequently, for each question, the relevant publications were organised into a number of “lines of evidence”

WoE table in hazard identification

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Table Y. Example of table used in the WoE approach

Question1: 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 based on previous assessments: ***Strength:*** ***Strength:*** ***Weakness:***			
Line of Evidence 1: increased effect on…… ***Strength:*** ***Weakness:*** ***Weakness:***			
Overall conclusion on Likelihood:			**Chosen likelihood level**

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

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Table V. 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

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

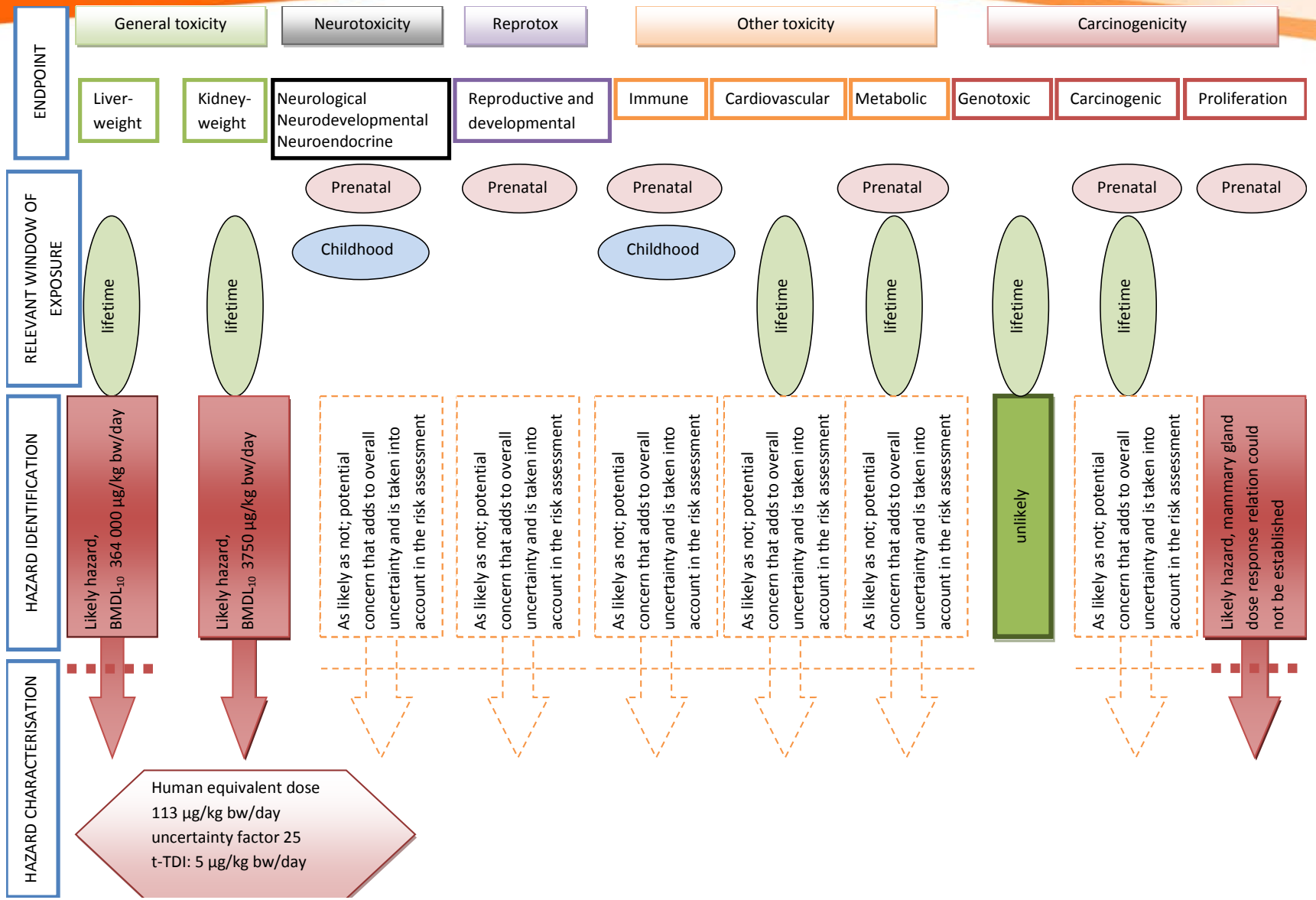
WoE: Example for mammary proliferation (without strengths and weaknesses)

Question 1 (Q1): 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 as reported by the study authors (Positive, Negative or Uncertain)	Reliability (Low, Medium or High)	Influence on Likelihood (see Table V)
Starting point based on previous assessments (EFSA, 2006, 2010): Based on the reviewed studies (Avecedo et al. 2013, Betancourt et al, 2010; Durando et al, 2007; Jenkins et al, 2009; Moral et al. 2008; Murray et al, 2007; Vandenberg et al, 2007; 2008) the implications of cell proliferation in the mammary gland and the significance of an increased cell proliferation/apoptosis ratio deserve further consideration. Additionally, the Panel noted the findings of a number of earlier s.c. studies (Nikaido et al, 2004, 2005; Markey et al, 2001, 2005; Munoz-de-Toro et al, 2005, Rubin et al, 2006) supporting this conclusion.	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 (Ayyanan et al., 2011, Tharp et al.,, 2012, Vandenberg, 2013; U.S. FDA/NCTR 90-day study, 2013, Acevedo 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.			**Likely** (for mammary gland proliferation)

Hazard identification

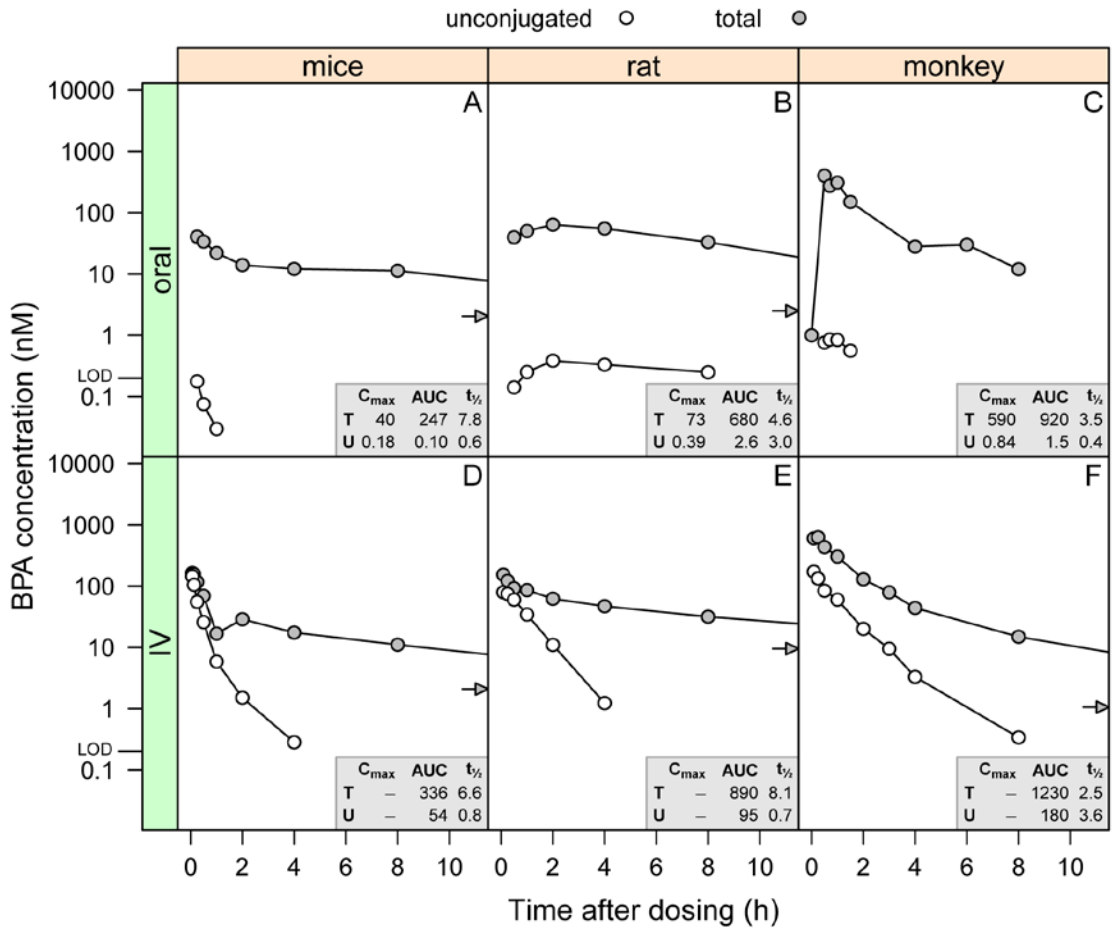
Overall likelihood

Overview of hazard identification



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

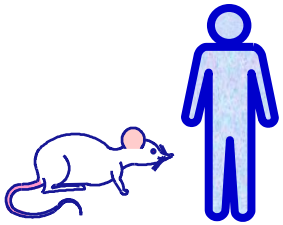
New study in mice, free BPA below LOD !!!

Uncertainty

Hazard identification - Oral human equivalent dose (HED)

- Derivation of a human-equivalent dose (HED) is an accepted method for linking a critical effect from the dose-response relationship in animals to predict a level without harmful effects in humans
- In derivation of the HED, the exposure related to the critical effect (i.e. a BMDL or a NOAEL) found in an animal study is multiplied by a factor that takes account of quantitative differences in toxicokinetics between the animal species used in the study and humans.
- Uses AUC to calculate Human Equivalent Dose adjustment Factor (HEDF)
  - HEDF = AUCanimal / AUChuman

100 - FOLD DEFAULT UNCERTAINTY FACTOR

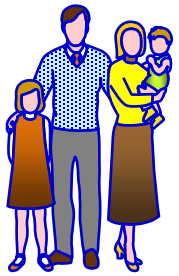


INTER-SPECIES DIFFERENCES

10 - FOLD

INTER-INDIVIDUAL DIFFERENCES

10 - FOLD



TOXICO-KINETIC	TOXICO-DYNAMIC	TOXICO-KINETIC	TOXICO-DYNAMIC
4	2.5	3.2	3.2

This default uncertainty factors for interspecies kinetics is already accounted for in the conversion of the animal dose into a HED, which is based on real data

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)	–

Hazard characterisation – Tyl et al. 2008

- Two generation study in CD-1 mice
- BPA in feed
- Doses 0, 0.003, 0.03, 0.3, 5, 50 and 600 mg/kg bw/day
- 17β-estradiol as positive control
- Systemic effects in adults were increased kidney and liver weight, centrilobular hepatocyte hypertrophy, and renal nephropathy and statistical significant reduction in epididymal sperm concentration (15% reduction) in both F0 and F1 males at (600 mg/kg bw per day)

Hazard characterisation

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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 observed for hepatocyte hypertrophy, the effect of BPA on hepatocyte hypertrophy was regarded by the Panel as adaptive and as a less critical effect than the effect in the kidney. The Panel has therefore selected the endpoint of 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.

Hazard characterisation – temporary-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

- Uncertainty factor of 25 to be applied to the mean HED of 113 µg/kg bw per day

- A **t-TDI** is derived for external oral exposure to BPA in humans of 4.5 µg/kg bw per day (rounded up to **5 µg/kg bw per day**), based on the kidney weight effect in the mouse.

Dermal exposure expressed as equivalent oral dose based on PBPK modelling

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

Population group in		DO	DD	AUCO	AUCD	D'D	D'D/DD
Exposure assessment	PBPK modelling	ng (kg bw)–1 d–1		pmol × h × l–1		ng (kg bw)–1 d–1	
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 expressed as equivalent oral dose (D'D) for **High** exposure

Population group in		DO	DD	AUCO	AUCD	D'D	D'D/DD
Exposure assessment	PBPK modelling	ng (kg bw)–1 d–1		pmol × h × l–1		ng (kg bw)–1 d–1	
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

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#	1152m#
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

Risk characterisation/2

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) 384.3(o) 510
Dermal high (d)	470 (d) 293 (o) 763	470 (d) 818 (o) 1 288	1152 (d) 161(o) 1 313	**1152 (d) 384.3(o) 1 536**

Dermal exposure contributes more than oral

The aggregated exposure for other children (1 288 ng/kg bw per day) and teenagers (1 543 ng/kg bw per day) will be approximately 3-4 fold below the proposed t- TDI of 5 µg/ kg bw/day

Draft conclusion

- The aggregated oral and dermal exposure is well below the t-TDI of 5 µg/kg bw per day even for the highest exposed groups in the population.

- Thus the health concern for BPA is low at the current level of exposure.

- These conclusions also apply to the offspring of mothers exposed during pregnancy and to the elderly.