Working group on food contact materials under PAFF section novel food and toxicological safety of the food chain (SANTE/E-2), 27 April 2023

Re-evaluation of the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs and protocol for the risk assessment strategy

EUROPEAN FOOD SAFETY AUTHORITY

EC REGULATORY UPDATE OF BPA IN FEB 2018

Following the 2015 BPA EFSA opinion :

→ EC amended the Plastics **Regulation (EU) No 10/2011** with lower limits for BPA in plastics

→ EC introduced new **Regulation (EU) 2018/213** applying the SML also to varnishes and coatings.

Plastic FCM: Reduction of the Specific Migration Limit (SML) for BPA from 0.6 mg/kg to 0.05 mg/kg of food

Plastic FCM: Extension of the ban on the use of BPA in the manufacture of polycarbonate baby bottles to sippy cups

Varnishes and coatings (e.g. interior of food cans): exceptional application of the same SML (0.05 mg/kg) as in plastics

Varnishes and coatings in articles specifically intended to come into contact with young children's food: SML of non-detect = NO migration (detection limit = 0.01 mg/kg) of BPA

Overview of previous EFSA evaluations on BPA

2015

Scientific opinion on BPA risk assessment (temporary-TDI: from 50 to 4 µg/kg bw per day)

2016

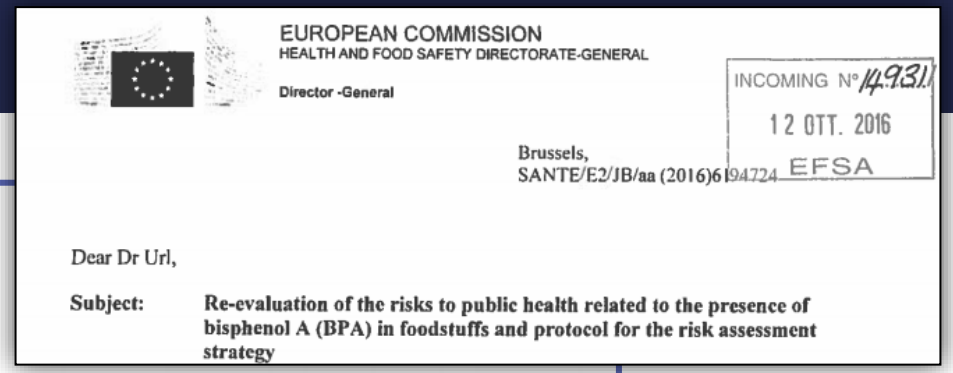
Statement on BPA immunotoxicity

2016

New two step-mandate on BPA hazard re-evaluation by EC to EFSA

3

MANDATE ON BPA'S RE-EVALUATION



EUROPEAN COMMISSION
HEALTH AND FOOD SAFETY DIRECTORATE-GENERAL
Director -General

INCOMING N° 14931
12 OTT. 2016
EFSA

Brussels,
SANTE/E2/JB/aa (2016)6194724

Dear Dr Url,

Subject: **Re-evaluation of the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs and protocol for the risk assessment strategy**

Annex

Terms of Reference

In accordance with Article 29(1)(a) of Regulation (EC) No 178/2002[2], the European Commission asks EFSA to:

Step 1

- establish a protocol detailing the criteria for new study inclusion and for toxicological evidence appraisal for the re-evaluation of BPA, to ensure an efficient and transparent re-assessment of BPA;

Step 2

- re-evaluate the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs. In particular, the re-evaluation should take into consideration new data available from the results of the US NTP/ FDA study due in 2017 as well as all other new available information not previously evaluated by EFSA and which fulfil the criteria laid down in an established protocol. This re-evaluation should seek to clarify the remaining uncertainties concerning the toxicological endpoints of BPA, especially those concerning the mammary gland, reproductive, metabolic, neurobehavioural and immune systems and to establish a full tolerable daily intake (TDI) on the basis of the new information available.

EC MANDATE (2016): TWO-STEP APPROACH

1st step: BPA hazard assessment protocol

Revisions of the methodology were applied before the full implementation

2nd step: Re-evaluation of BPA safety

- Seek to clarify the remaining uncertainties
- Take into consideration new data from the US NTP/FDA study, as well as all other new available information

Finalised

(draft opinion endorsed on 24 Nov 2021; final opinion adopted on 6 Dec. 2022 and published on 19 Apr. 2023)

PROTOCOL: SYSTEMATIC APPROACH

1. Problem formulation
2. Literature search & selection studies
3. Appraisal of the internal validity
4. Appraisal of the external validity
5. Data extraction
6. Weighing the body of evidence
7. Selection of the effects for HC
8. Uncertainty analysis

Literature collected until Oct 2018 (+ NTP Grantees studies published afterwards)
Genotoxicity: literature collected until July 2021

PUBLIC CONSULTATION – DRAFT OPINION BPA

- **24 November 2021**

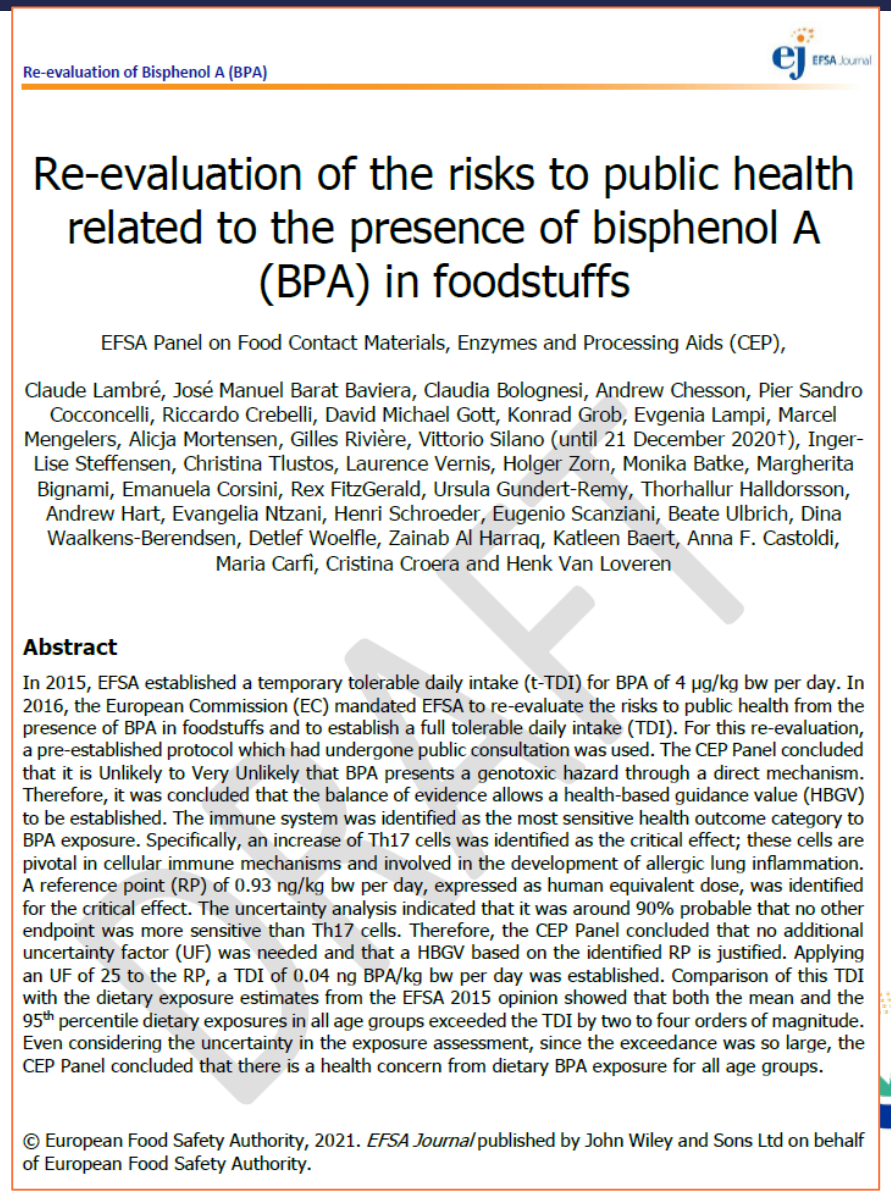
  The EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (CEP) **endorsed for public consultation** the draft scientific opinion.

- **15 December 2021 to 22 February 2022**

  Public consultation open

  Interested parties submitted comments using the dedicated EFSA webpage.

  https://connect.efsa.europa.eu/RM/s/publicconsultation2/a0l1v00000E8BRD/pc0109



EFSA Journal

Re-evaluation of the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs

EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (CEP),

Claude Lambré, José Manuel Barat Baviera, Claudia Bolognesi, Andrew Chesson, Pier Sandro Cocconcelli, Riccardo Crebelli, David Michael Gott, Konrad Grob, Evgenia Lampi, Marcel Mengelers, Alicja Mortensen, Gilles Rivière, Vittorio Silano (until 21 December 2020†), Inger-Lise Steffensen, Christina Tlustos, Laurence Vernis, Holger Zorn, Monika Batke, Margherita Bignami, Emanuela Corsini, Rex FitzGerald, Ursula Gundert-Remy, Thorhallur Halldorsson, Andrew Hart, Evangelia Ntzani, Henri Schroeder, Eugenio Scanziani, Beate Ulbrich, Dina Waalkens-Berendsen, Detlef Woelfle, Zainab Al Harraq, Katleen Baert, Anna F. Castoldi, Maria Carfi, Cristina Croera and Henk Van Loveren

Abstract

In 2015, EFSA established a temporary tolerable daily intake (t-TDI) for BPA of 4 µg/kg bw per day. In 2016, the European Commission (EC) mandated EFSA to re-evaluate the risks to public health from the presence of BPA in foodstuffs and to establish a full tolerable daily intake (TDI). For this re-evaluation, a pre-established protocol which had undergone public consultation was used. The CEP Panel concluded that it is Unlikely to Very Unlikely that BPA presents a genotoxic hazard through a direct mechanism. Therefore, it was concluded that the balance of evidence allows a health-based guidance value (HBGV) to be established. The immune system was identified as the most sensitive health outcome category to BPA exposure. Specifically, an increase of Th17 cells was identified as the critical effect; these cells are pivotal in cellular immune mechanisms and involved in the development of allergic lung inflammation. A reference point (RP) of 0.93 ng/kg bw per day, expressed as human equivalent dose, was identified for the critical effect. The uncertainty analysis indicated that it was around 90% probable that no other endpoint was more sensitive than Th17 cells. Therefore, the CEP Panel concluded that no additional uncertainty factor (UF) was needed and that a HBGV based on the identified RP is justified. Applying an UF of 25 to the RP, a TDI of 0.04 ng BPA/kg bw per day was established. Comparison of this TDI with the dietary exposure estimates from the EFSA 2015 opinion showed that both the mean and the 95th percentile dietary exposures in all age groups exceeded the TDI by two to four orders of magnitude. Even considering the uncertainty in the exposure assessment, since the exceedance was so large, the CEP Panel concluded that there is a health concern from dietary BPA exposure for all age groups.

ENGAGEMENT ACTIVITIES

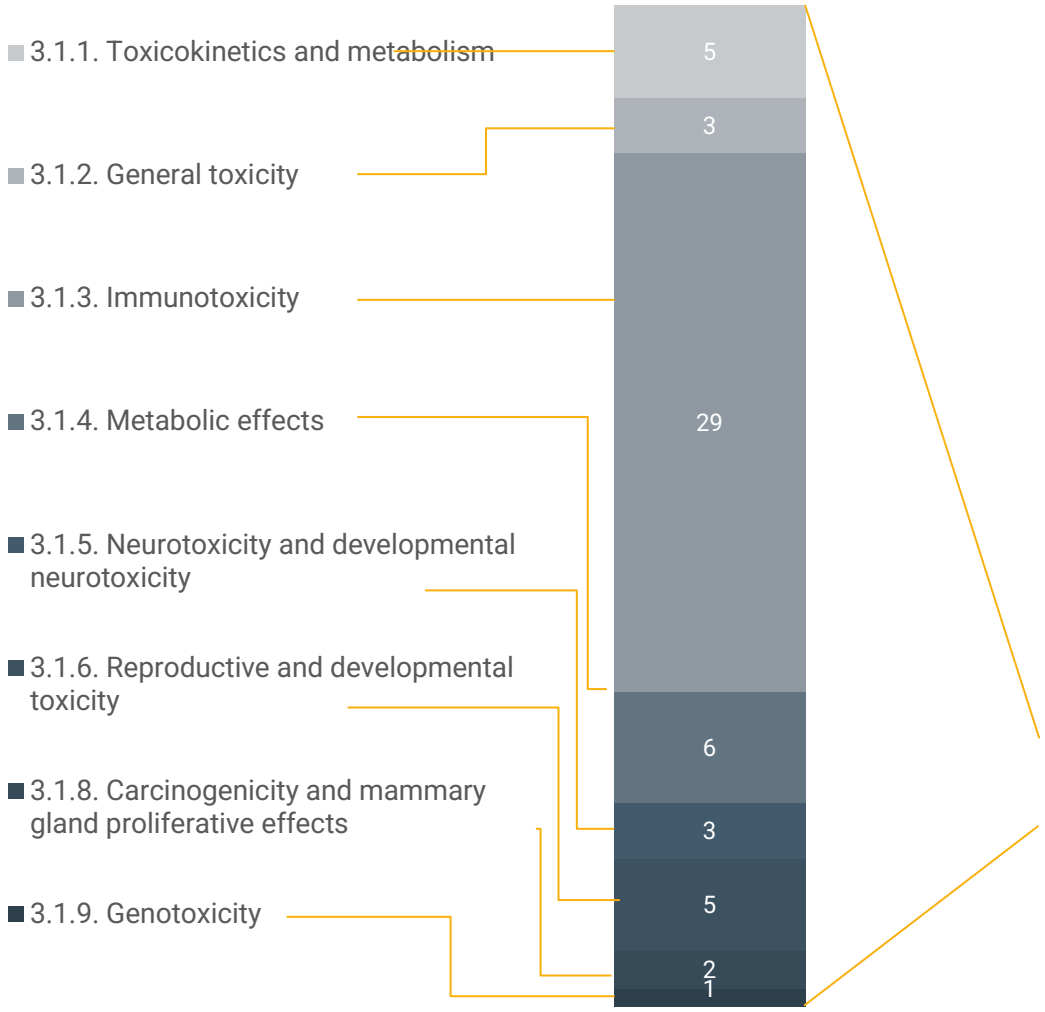
- **Stakeholders and interested parties:** public meeting on 24 Jan. 2022
- **EU Member states:** 25 Jan. 2022
- **US FDA:** 7 Feb. 2022
- **European Medicines Agency:** 16 Feb, 29 Nov 2022
- **EFSA Scientific Committee:** 22 and 28 April 2022
- **Thematic workshop on biomarkers of effects:** 22-23 Sept. 2022

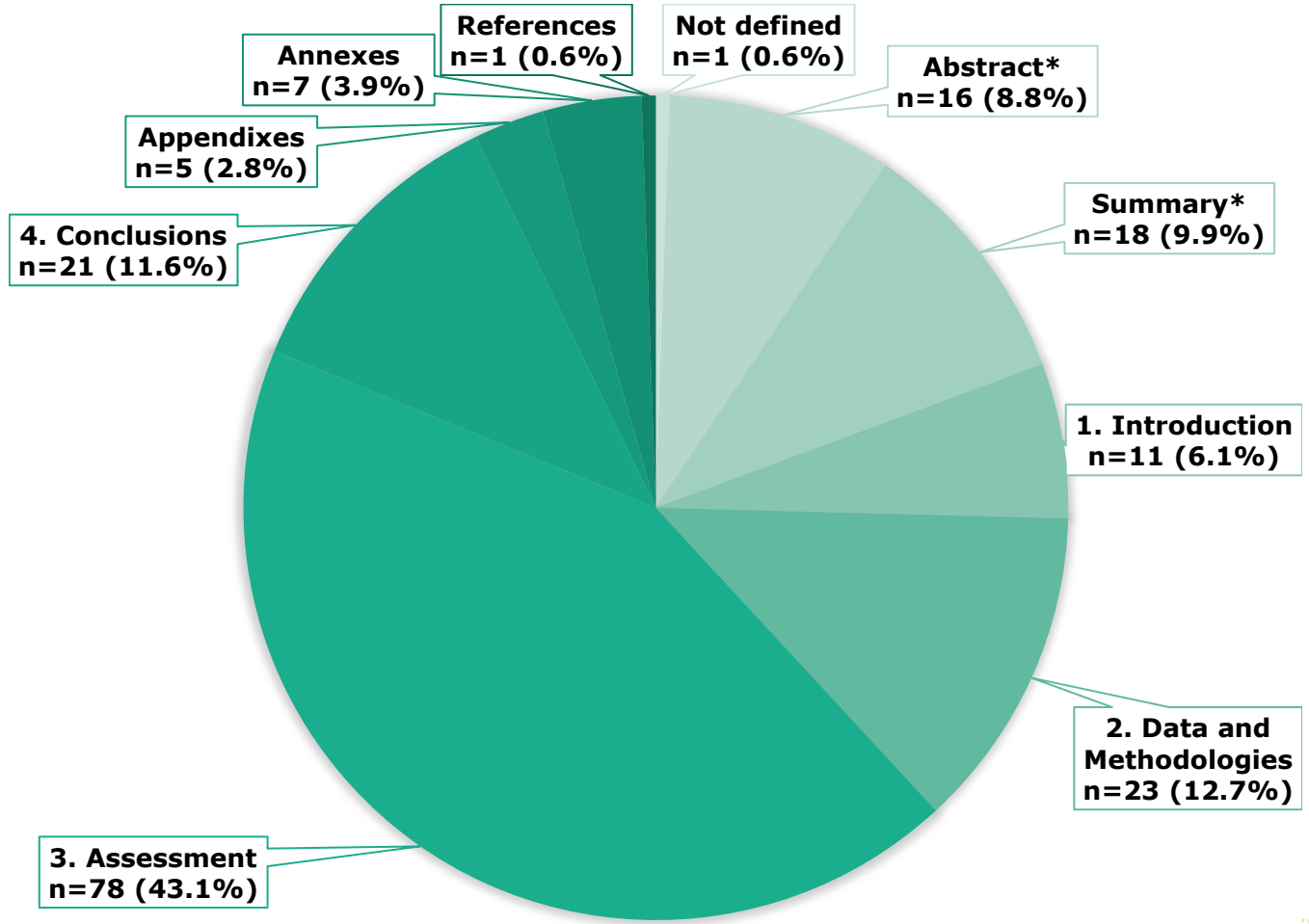
Comments received from the Public Consultation

- Comments submitted by **62 interested parties from 21 countries**
  Individual companies, industry organisations, scientific associations, public agencies, university, NGOs, consultancy firms, individuals in their personal capacity and anonymous contributors
  - 46 interested parties submitting on behalf of affiliation/organisation
  - 16 interested parties submitting on personal capacity

- 301 comments received in total, out of which:
  - **181 unique comments containing one or more issues**
    ⇨ responded on a one-by-one basis
  - 96 duplicate comments
  - 19 empty comments
  - 5 comments outside the remit of the opinion

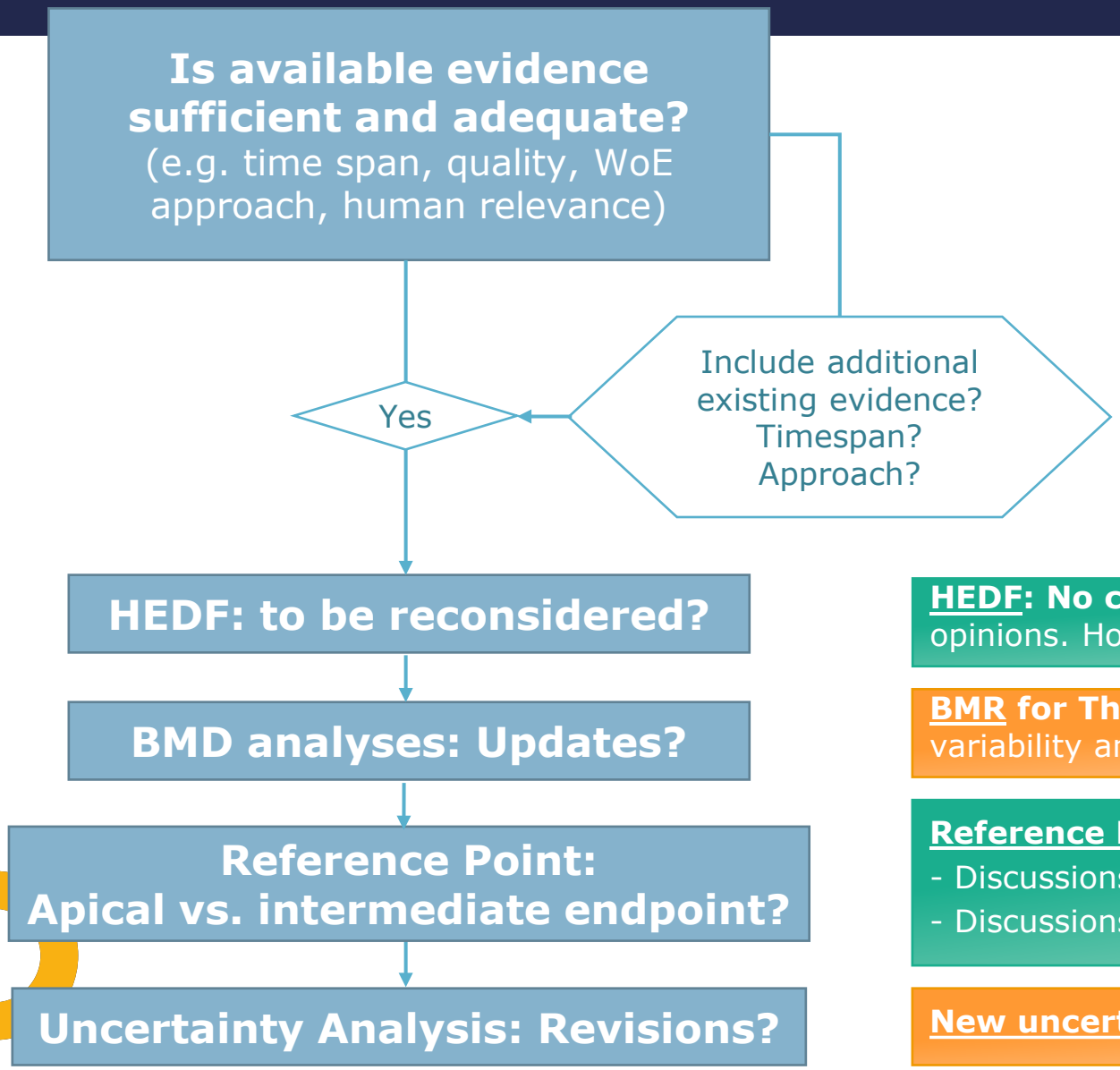
SECTION DISTRIBUTION OF PUBLIC COMMENTS (N=181)





* Including general comments

OVERVIEW OF MAIN POINTS ADDRESSED IN RESPONSE TO PC



Evidence: clarifications added to revised opinion including:
- Mechanisms & relevance of reference point.
- Relevance of epidemiological studies.

Quality of studies & WoE: No major changes to opinion.
However, discussed in response to public comments and taken into account in new UA.

Time-span: No major changes to opinion, however:
Evidence before 2013: More details given on how outcome of previous opinions were taken into account in HI conclusion chapters.
Evidence after 2018: Discussed in response to public comments and in revised opinion regarding grouping and mechanistic issues.

HEDF: No changes to opinion, based on information from previous EFSA opinions. However, further clarifications given and considered in the new UA.

BMR for Th17 cells modified from 20% to 40% to take into account human variability and the plasticity of the immune system -> impact on BMDL.

Reference Point: No major changes to opinion, however:
- Discussions on the effects from other HOCs also noted at doses close to the RP.
- Discussions on the lack of guidance on how to use intermediate endpoint in RA.

New uncertainty analysis taking into account public comments received.

BPA re-evaluation: problem formulation

- **Aim** of this hazard assessment:

To assess whether the new scientific evidence still supports the previous t-TDI for BPA of 4 µg/kg bw per day.

- Decision should be based on the evaluation of:
  - (i) **adverse effects in humans** associated with the exposure to BPA via any route;
  - (ii) **adverse effects in animals** after exposure to BPA via any route;
  - (iii) human and animal **toxicokinetics** of BPA

Health Outcome Categories assessed

- Assessed endpoints were grouped into structural and/or functional clusters **for eight health outcome categories** (HOCs):

  - General toxicity
  - Immunotoxicity
  - Metabolic effects
  - Neurotoxicity and developmental neurotoxicity
  - Reproductive and developmental toxicity
  - Cardiotoxicity
  - Carcinogenicity and mammary gland proliferative effects
  - Genotoxicity

Hazard Identification

IMMUNOTOXICITY HAZARD IDENTIFICATION: INTEGRATED LIKELIHOOD

Human stream		Animal stream		Integrated likelihood
Cluster	Overall likelihood	Cluster	Overall likelihood	
Asthma/ allergy	ALAN (P, C)	**Allergic lung inflammation**	**Likely** (D, A)	**Likely**
		Cellular immunity	**Likely** (D)	**Likely**
		Inflammation	**Likely** (G)	**Likely**
		Humoral immunity	ALAN (D)	ALAN
		Innate immunity	ALAN (D)	ALAN

P: Exposure during pregnancy
C: Exposure during childhood

D: Developmental (pre- / post-natal until weaning) exposure
G: Growth phase / young age exposure
A: Adult exposure

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY HAZARD IDENTIFICATION: INTEGRATED LIKELIHOOD

Human stream		Animal stream		Integrated likelihood
Cluster	Overall likelihood	Cluster	Overall likelihood	
		Developmental toxicity	ALAN (D, D&A,G)	ALAN
Fetal and Post-natal Growth	Not Likely (P)			Not Likely
Pubertal/Endocrine	ALAN (P)			ALAN
Female fertility	ALAN (A)	**Female reproductive toxicity**	**Likely** (D,D&A,G,A)	**Likely**
Male fertility	Not Likely (A)	**Male reproductive toxicity**	**Likely** (D&A,G,A)	**Likely**
Prematurity	Not Likely (P)			Not Likely
Pre-eclampsia	ALAN			ALAN

P: Exposure during pregnancy
C: Exposure during childhood
A: Adult exposure

D: Developmental (pre- / post-natal until weaning) exposure
D&A: Developmental until adulthood exposure
G: Growth phase / young age exposure
A: Adult exposure

METABOLIC EFFECTS HAZARD IDENTIFICATION: INTEGRATED LIKELIHOOD (1/2)

Human stream		Animal stream		Integrated likelihood
Cluster	**Overall likelihood**	**Cluster**	**Overall likelihood**	
Obesity	ALAN (A)	**Obesity**	ALAN (D, D&A, G)	ALAN
Thyroid effects	Not Likely (P)	**Thyroid hormones**	Not Likely (D, D&A, A)	Not Likely
Cardiometabolic effects	Not Likely (P)			Not Likely
T2DM	ALAN (A)			ALAN
Gestational Diabetes Mellitus	Not Likely (A)			Not Likely

P: Exposure during pregnancy;
C: Exposure during childhood;
A: Adult exposure

D: Developmental (pre-/post-natal until weaning) exposure
D&A: Developmental until adulthood exposure
G: Growth phase / young age exposure
A: Adult exposure
I: Indirect (germline) exposure

METABOLIC EFFECTS HAZARD IDENTIFICATION: INTEGRATED LIKELIHOOD (2/2)

Human stream		Animal stream		Integrated likelihood
Cluster	Overall likelihood	Cluster	Overall likelihood	
		Uric Acid	**Likely (A)**	**Likely**
		T1DM	ALAN (G, A)	ALAN
		Fat deposition in the liver	ALAN (D, G, A)	ALAN
		Glucose regulation	ALAN (D, A, I)	ALAN
		Blood lipids	ALAN (A)	ALAN
		Other metabolic hormones	Not Likely (D, D&A, G, A)	Not Likely

P: Exposure during pregnancy;
C: Exposure during childhood;
A: Adult exposure

D: Developmental (pre-/post-natal until weaning) exposure
D&A: Developmental until adulthood exposure
G: Growth phase / young age exposure
A: Adult exposure
I: Indirect (germline) exposure

NEUROTOXICITY AND DEVELOPMENTAL NEUROTOXICITY HAZARD IDENTIFICATION: INTEGRATED LIKELIHOOD

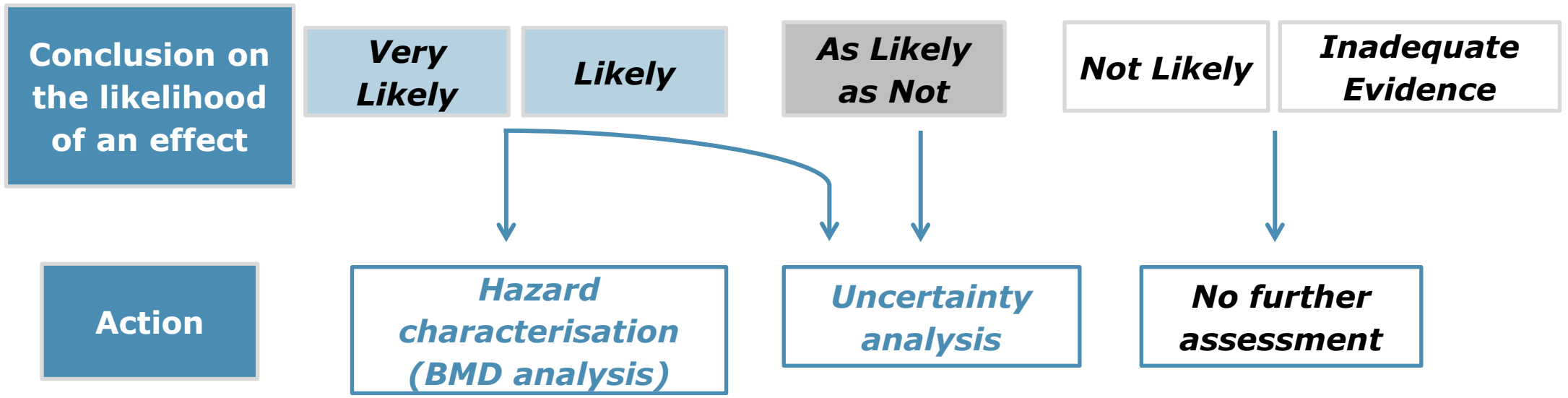
Human stream		Animal stream		Integrated likelihood
Cluster	Overall likelihood	Cluster	Overall likelihood	
Neurodevelopment (behaviour after developmental exposure)	Not likely (P)	**Behaviour**	**Likely** (D, G, A, I)	**Likely**
		Neuromorphology	**Likely** (D, G)	**Likely**
		Nervous system functionality	**Likely** (A)	**Likely**

P: Exposure during pregnancy
C: Exposure during childhood

D: Developmental (pre- / post-natal until weaning) exposure
G: Growth phase / young age exposure
A: Adult exposure
I: Indirect (germline) exposure

Hazard characterisation

SELECTION OF THE EFFECTS FOR THE HAZARD CHARACTERISATION AND THE UNCERTAINTY ANALYSIS (UA)



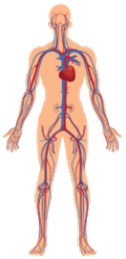
- Studies investigating **Very likely** or **Likely effects**, with at least 1 ctrl+ two BPA dose levels, were considered for **benchmark dose (BMD) analysis.**

- All **ALAN, Likely** and **Very likely** clusters were included in the **uncertainty analysis (UA).**

TOXICOKINETICS: SELECTION OF THE HEDF

- The CEP Panel decided to use the **median value of the AUCs from two human studies** for the calculation of the **Human Equivalent Dose Factor (HEDF)**.
- **AUC data for mice** were used from the 2015 EFSA opinion (EFSA CEF Panel, 2015)

Species (oral route)	AUC (nM × h)	HEDF (AUC animal/ AUC human)
Human (Thayer et al., 2015 and Teeguarden et al., 2015) (median)	15.7	
Mouse (Doerge et al., 2011)	0.244	0.0155



ENDPOINTS BROUGHT FORWARD FOR SELECTION REFERENCE POINT (RP)

Immuno-toxicity	• Effect on Th17 cells • Effect on neutrophils in epididymis • Effect on OVA specific IgE
Metabolic effects	• Hepatic uric acid
Neurotoxicity and developmental neurotoxicity	• Anxiety/emotionality • Learning and memory • Dendritic spine density
Reproductive and developmental toxicity	• Ovary weight • Ovary histology • Epididymis histology • Effects on sperm

BMD ANALYSES (BASED ON 2017 EFSA GUIDANCE)

- Of all endpoints considered for the identification of a RP, the effect of BPA on Th17 cells in mice was the most sensitive (i.e. lowest BMDL)

- Besides the immunotoxicity study, also studies in other health outcome categories, i.e. in reproductive toxicity (ratio of primordial and total follicles, sperm motility) and metabolism (uric acid), had BMDLs within a range of up to 7-fold higher compared to the BMDL for Th17 cells

Critical endpoint, Species	***BMDL (HED)***	***Reference***
Th17 cells, Mice	**8.2 ng/kg bw per day**	**Luo et al., 2016**
Hepatic uric acid, Mice	24.6 ng/kg bw per day	Ma et al., 2018
Primordial/Total follicles ratio, Mice	44 ng/kg bw per day	Hu et al., 2018
Sperm motility, Mice	53 ng/kg bw per day	Wang et al., 2016

UNCERTAINTY ANALYSIS

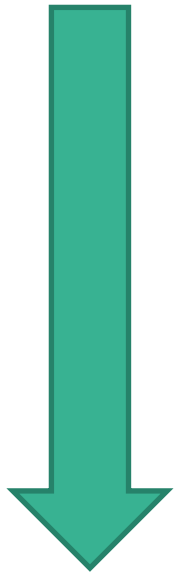
- The uncertainty analysis was conducted **in accordance with EFSA's guidance on uncertainty analysis**, using a combination of methods appropriate to each step of the assessment (EFSA Scientific Committee, 2018).

Aim →

To assess whether other effects of BPA may potentially occur after exposure to lower doses than the endpoint on which the reference point (RP) is based and, if so, inform a decision on what size of additional uncertainty factor would be suitable to take those effects into account.

HEALTH-BASED GUIDANCE VALUE (HBGV)

Reference point (RP) for the critical effect: **8.2 ng/kg bw per day**, expressed as human equivalent dose



Default UFs of 25

- inter-species toxicodynamic difference (2.5)
- intra-human variability in toxicokinetics and toxicodynamics (10)

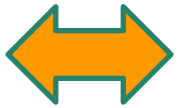
Uncertainty analysis: additional UF of 2

Tolerable daily intake (TDI) = **0.2 ng BPA/kg bw per day**

Risk characterisation

MAIN FINDINGS: RISK CHARACTERISATION

TDI: 0.2 ng BPA/kg bw per day



Dietary exposure estimates EFSA 2015 Opinion

Both the average and high **dietary exposures** in all age groups **exceeded the TDI** by two to three orders of magnitude

- Even considering the uncertainty in the exposure assessment, since the exceedance was so large, the CEP Panel concluded that **there is a health concern** from dietary BPA exposure for all age groups of the general population.


THANK YOU

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