This is a background paper for discussion. It has not been finalised and should not be cited.

TOX/2023/50

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT)

Third draft interim position statement on bisphenol A

Introduction

1. In April 2023, the EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (CEP) established a new tolerable daily intake (TDI) of 0.2 ng BPA/kg bw per day. Although this new TDI is higher than the initially proposed level of 0.04 ng/kg bw, mean and high-level consumers for all age groups would exceed the new TDI by 2-3 orders of magnitude.

2. The COT discussed the draft EFSA opinion at their extraordinary meeting in February 2023 and provided comments on the public consultation. The final EFSA opinion and diverging opinions by the EMA and the BfR were discussed at their May 2023 meeting.

3. A draft interim position statement was presented to the Committee in May and following discussion, again at the September 2023 meeting. Following comments by the Committee in September Annex A provides the third draft interim position statement.

4. In the UK Annex II of retained regulation 2018/213 on the use of bisphenol A in varnishes and coatings intended to come into contact with food and amending Regulation (EU) No 10/2011 as regards the use of that substance in plastic food contact materials sets out the current specific migration limit (SML) for BPA of 0.05 mg/kg. The same SML applies to varnished and coated food contact materials.

This is a background paper for discussion. It has not been finalised and should not be cited.

Health Based Guidance Values

5. At the September COT meeting Members enquired about health-based guidance values (HBGVs) by European or international authorities. The available HBGVs and other relevant information have been summarised in the following paragraphs.

6. Based on the lowest NOAEL of 25 mg/kg bw per day observed in a 90 day carcinogenesis study in rats from the US National Toxicology Program (NTP), Health Canada set a provisional tolerable daily intake (pTDI) of 25 µg/kg bw per day. The pTDI was upheld in 2008, and exposure assessment showed that the probably daily intake of BPA for the general population was 0.18 µg/kg bw per day, and 1.35 µg/kg bw per day for infants. While, based on the overall weight of evidence, Health Canada concluded that the current dietary exposure to BPA through food packaging uses is not expected to pose a health risk to the general population, including newborns and children, they did note that the neurodevelopmental and behavioural dataset in experimental animals suggests a heightened sensitivity during stages of development in rodents. Since 2008, Health Canada has undertaken a number of surveys to measure BPA levels and an updated exposure assessment in 2012 showed exposures approximately three times lower than those reported in 2008.

7. As the Committee is aware, the Bundesamt fuer Risikobewertung (BfR) published their diverging view from EFSA in 2023. Based on the detailed analysis of the scientific data on BPA (from the EFSA opinion), the BfR derived a TDI of 0.2 µg/kg bw per day (equivalent to 200 ng/kg bw per day). This TDI is 20-times lower than EFSA's previous provisional TDI, derived in 2015. Since current exposure estimates for the German or European population are not available, the BfR recommends to collect and evaluate additional and more current exposure data. The full risk assessment can be found at: Bisphenol A: BfR proposes health based guidance value, current exposure data are needed for a full risk assessment - BfR Opinion No 018/2023 issued 19 April 2023 (bund.de).

8. Food Standards Australia and New Zealand (FSANZ) refers to the NTPs CLARITY study in reference to their assessment of BPA and note that extremely large amounts of foods and beverages would need to be consumed to reach the TDI for BPA. For example a nine month old baby (9 kg) would have to eat more than 1 kg of canned baby custard containing BPA at the highest level found (420 parts per billion; found in a survey). FSANZ concluded that the European (EU) restrictions, which took effect in September 2018, reducing the specific migration limit (SML) for BPA in plastic food contact materials (FCM) from 0.6 to 0.05 mg/kg food, were not based on an identified health risk and did not indicate a health concern for Australia and New Zealand consumers. In addition, in 2010 the Australian Government had announced a voluntary phase out of BPA use in polycarbonate baby bottles. A survey undertaken in 2016 found that dietary exposures of Australian consumers were low and within acceptable safe limits. The Secretariat was unable to find which TDI FSANZ used in their evaluation.

9. The US FDA upheld their no observed adverse effect level (NOAEL) of 5 mg/kg bw per day (via oral exposure) in 2014, following the evaluation of new data. At the time the US FDA did not consider there to be a risk to human health from exposure to BPA.

10. The US EPA provides only general information on BPA on their website but does note that they are working with the US FDA and NIEHS on an action plan for BPA.

11. The French Scientific Assessment Agency for Food and Nutrition (ANSES) noted in their 2013 assessment Dossier de presse (anses.fr) that under certain circumstances the exposure of pregnant women to BPA could pose a potential risk to the unborn child. After examining EFSAs 2017 (draft) opinion, ANSES considered the conclusions of its own 2013 assessment to remain valid and believed it necessary to pursue active monitoring to update the data on BPA. ANSES notes EFSAs mandate to update the assessment on BPA but no further information is currently available on ANSES' stance on the EFSA 2023 opinion.

12. The Dutch National Institute for Public Health and the Environment (RIVM) noted in 2016 that based on new insights the current EU standards required revisiting and to reduce BPA exposure in the short term wherever possible. Special attention should thereby be given to protecting small children, pregnant women and women who breastfeed as the developing unborn child, infants and young children are more sensitive to the effects of BPA than adults. The RIVM published a report on BPA (Part 1) in 2014, providing an overview of the current state of knowledge about BPA, Part 2 of the report aimed to evaluate the scientific knowledge and discuss possible health risk. The Secretariat was unbale to find Part 2, or any information as to whether it had been published in 2015, as anticipated/planned.

13. Additionally, the EU Environment Agency provides an overview of BPA, but no HBGVs or commentary on the EFSA 2023 evaluation. A paper by Choi et al. (2010) suggested a TDI for Korea of 0.05 mg/kg bw per day, based on a point of departure (POD) from rat and mice reproductive studies by Tyl et al. (2002, 2006). The POD was a NOAEL of 5 mg/kg bw per day for systemic toxicity. The paper by Choi also included a table providing HBGVs by EFSA (2015), Health Canada and the US EPA. The Secretariat was unable to find the source of the TDI for the US EPA.

Question on which the views of the Committee are sought

i. Do Members have any comments on the information/HBGVs provided by other authorities, i.e. does the Committee consider any of the provided HBGVs applicable as an interim measure until their own assessment of BPA has concluded?

ii. Do Members have any comments on the draft interim position paper?

iii. Does the Committee have any further comments?

Secretariat
October 2023

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TOX/2023/51 Annex A

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT)

Third draft interim position paper on bisphenol A

Introduction and background

1. The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) reviewed the scientific basis and implications for risk management of the new EFSA tolerable daily intake (TDI) for bisphenol A (BPA).

2. BPA is used in food contact materials such as reusable bottles, tableware and storage containers, in thermal printing in certain paper products and for protective linings of food and beverage cans and vats (EFSA, 2021). BPA is authorised for use in plastic food contact materials and a specific migration limit of 0.05 mg/kg was set in the European Union (EU) and United Kingdom (UK), following the European Food Safety Authority's (EFSA) 2015 evaluation of BPA.

3. The temporary TDI (tTDI) established by EFSA in 2015 of 4 µg/kg body weight (bw)/day was based on increased mean relative kidney weight in animal studies and a human equivalent dose (HED). Based on the 2015 exposure assessment EFSA concluded that there was no health concern for any age group from dietary exposure and low health concern from aggregate exposure. However, EFSA noted considerable uncertainties in the exposure estimate from non-dietary sources.

4. In 2016, EFSA received a mandate from the European Commission to re-evaluate the risk to public health related to the presence of BPA in foodstuffs. The

re-evaluation should take into consideration data that became available since the last assessment and should seek to clarify the remaining uncertainties concerning the toxicological endpoints of BPA.

14. The COT discussed the draft EFSA opinion at their extraordinary meeting in February 2023 and provided comments to EFSA. The final EFSA opinion and diverging opinions by the EMA and the BfR were discussed at the May 2023 meeting.

2023 EFSA evaluation

5. For the derivation of their new TDI, the European Food Safety Authority (EFSA) Panel on Food Contact Materials, Enzymes and Processing Aids (CEP) assessed the evidence from animal data and human observational studies and identified the immune system as the most sensitive endpoint to BPA. An increase in the percentage of TH17 cells in mice, cells which are critical for immune mechanisms and involved in inflammatory conditions, was considered as the most sensitive endpoint and hence the critical effect of BPA.

6. The new tolerable daily intake (TDI) of 0.2 ng BPA/kg bodyweight (bw) per day was based on a human equivalent dose (HED) of 8.2 ng/kg bw per day, converted from the lowest $BMDL_{40}$ of an increase in the percentage of TH17 cells in mice. EFSA applied an overall uncertainty factor (UF) of 50, the default UF of 2.5 and 10 for interspecies toxicodynamic differences and intraspecies variability in toxicokinetics and toxicodynamics, respectively. No uncertainty factor was applied for inter species variability in toxicokinetics as this was already accounted for in the conversion to the HED. EFSA did however apply an additional UF of 2 based on the uncertainty analysis performed.

7. Although this new TDI is higher than the level of 0.04 ng/kg bw proposed in the draft opinion, based on the exposure assessment performed by EFSA in 2015,

mean and high-level consumers of all age groups could potentially exceed the new TDI by 2-3 orders of magnitude.

8. Both, the European Medical Agency (EMA) and the Bundesamt fuer Risikobewertung (BfR) provided comments to EFSA, highlighting their diverging views from EFSA, i.e., on the use of an intermediate endpoint for the derivation of a health-based guidance value (HBGV), the approach and timeframe applied for consideration of studies, and the risk assessment approach including the uncertainty analysis and clinical relevance/extrapolation from animals to humans and derivation of the HED. As the diverging views could not be resolved, EFSA and the EMA/BfR are obliged to present a joint document to the European Commission clarifying the contentious scientific issues and identifying relevant uncertainties in the data.

COT view

9. The final EFSA opinion and diverging views by the EMA and BfR were discussed by the COT at their May 2023 meeting. The COT noted that the scientific issues raised by the EMA and BfR aligned with the concerns and comments highlighted by the COT during the public consultation and May meeting.

10. The Committee considered that there was a lack of transparency on how the evidence had been integrated to derive the point of departure for the derivation of a HBGV.

11. EFSA utilized a predetermined protocol which restricted their inclusion of studies and subsequent data evaluation to a specific time period. While the Committee acknowledged that due to its size, it would not be feasible to assess the full database on BPA, and other studies would likewise have uncertainties, there was a wider data set available for BPA, which should have been considered in the evaluation for the relevant endpoint selection but also the derivation of the human equivalent dose (HED) factor. The Committee further queried whether an intermediate endpoint would be sufficiently robust to derive a HBGV but specifically

did not agree with EFSA's assessment that the increase in percentage of Th17 cells was a scientifically relevant and robust intermediate endpoint to be applied to the derivation of a new HBGV. Given the uncertainties over the endpoint a more robust weight of evidence approach and evidence integration should have been applied to a wider dataset to derive a more reliable and relevant endpoint on which to base the HBGV.

12. EFSA (2015) previously compared the temporary TDI (t-TDI) with exposure estimates and concluded that there was no health concern for any age group from dietary exposure and low health concern from aggregate exposure. In the current opinion EFSA was not explicitly asked to perform an exposure assessment and hence used the assessment from 2015, noting that the data used may not accurately reflect the current exposures to consumers. The COT agreed with the uncertainties in this approach and noted that work has been undertaken by industry to lower exposures to BPA and hence, the previous data may not be reflective of the current exposures.

Conclusions and next steps

13. The Committee noted that the current UK TDI is substantially above the new TDI established by EFSA. However, while the Committee considered it possible that the TDI would need to be revised to account for new evidence and ensure it was sufficiently protective, on balance the weight of evidence did not support the conclusions drawn by EFSA, or a TDI as low as that derived by EFSA. The Committee had concerns about the endpoint selected and noted that there were effects apparent in other endpoints, which would need to be considered. The Committee will therefore undertake their own weight of evidence approach and perform a transparent data integration, utilising the guidance on the synthesis of epidemiological and toxicological evidence (SETE), where applicable.

14. While the COT acknowledges that given the size of the database, this will not be a short undertaking, the work will aim at identifying key endpoints, gaps and

uncertainties and suggest a way forward on a robust point of departure from which to derive a TDI.

COT position paper

October 2023