Meeting

Fifth Draft Interim Position Statement on Bisphenol A

This is a paper for discussion.

This does not represent the views of the Committee and should not be cited.

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. Following their diverging view from EFSA the Bundesinstitut fuer Risikobewertung (BfR) published a full assessment of BPA in 2023, deriving a TDI of 0.2 µg/kg bw per day (equivalent to 200 ng/kg bw per day).

2. Following discussions of the EFSA opinion, a draft interim position statement by the COT was presented to the Committee in May, September and October 2023. Following the publication and discussions of the BfR assessment at the December meeting and internal discussions with policy colleagues an updated draft interim position statement was further presented at the February 2024 meeting.

3. At the February 2024 meeting, the Committees agreement to adopt the BfR TDI. The following interim position statement has therefore been updated to reflect the COTs conclusion and to include further detail underpinning said conclusion. Please note that significant changes/additions to the text have been highlighted in green.

Question on which the views of the Committee are sought:

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

ii. Does the Committee have any further comments?

Secretariat

March 2024

TOX/2024/13 Annex 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 European Food Safety Authority (EFSA) tolerable daily intake (TDI) for bisphenol A (BPA), **and the subsequent assessment by the Bundesinstitut fuer Risikobewertung (BfR).**

2. BPA is used and authorised in food contact materials (FCMs) 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. It is prohibited in coatings and varnishes applied to FCMs intended for infants and young children and operators must observe the no migration rule. Where it is permitted, operators must ensure that it observes the specific migration limit (SML) of 0.05 mg/kg (EFSA, 2021). The SML set in the European Union (EU) and United Kingdom (UK) was based on the 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 observed in animal studies and employed 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 (diet and house dust for the oral route, thermal paper and cosmetics for the dermal route). 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.

4. The COT discussed the draft EFSA opinion at their extraordinary meeting in February 2022 and provided comments to EFSA. The final EFSA opinion and diverging opinions by the European Medical Agency (EMA) and the Bundesinstitut fuer Risikobewertung (BfR) were discussed at the May 2023 meeting.

5. Following their diverging views from EFSA the BfR published their own assessment. The COT discussed the BfR assessment as well as the differences between EFSA and BfR in modelling and derivation of a human equivalent dose and TDI at their December 2023 meeting.

2023 EFSA Evaluation

5. For the derivation of their new TDI, the 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, a type of white blood cells was reported in mice treated with BPA. The reported increase in these cells, which are critical for immune mechanisms and are involved in inflammatory conditions, was considered as the most sensitive endpoint and hence the critical effect of BPA. While EFSA agreed that there is no direct causal link between the observed increase in TH17 cells and an allergy response, they noted that there is evidence of a link between Th17 cells (an intermediate endpoint, i.e. not the final toxic effect) and adverse outcomes, as changes in Th17 cells are involved in diseases with inflammatory pathogenesis, e.g. psoriasis, asthma.

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 confidence level of the benchmark dose (BMDL40) 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 EMA and the 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.

2023 BfR Assessment

9. Following their divergence with EFSA, the BfR published their own assessment of BPA in 2023.

10. A comprehensive systematic literature review was undertaken. The reliability of the studies was assessed based on pre-defined parameters and the studies were grouped into three tiers reflecting the respective weight of evidence (WoE). It should however be noted that the literature evaluation and evaluation was limited to the critical endpoints identified by EFSA, i.e. reproductive toxicity, immunological effects, increased serum uric acid, and toxicokinetics. For their assessment the BfR also considered the literature and data from the EFSA 2015 and 2023 assessments.

11. The BfR considered the immunological studies to be inconsistent regarding effects size and dose as well as suffering from shortcomings in design and reporting. Given that the increase in Th17 cells only represents an intermediate endpoint, for which a causal link to apical effects in a dose range relevant to humans is unclear, the BfR considered the immunological effects in humans, if they occur, unlikely to result from BPA in the exposure range of the EFSA TDI. Hence, the BfR considered effects on the male reproductive system (e.g. decreased sperm count and mobility, changes to testis histology) as the most sensitive endpoint and based its TDI derivation on reduced sperm count observed in two studies in rats. The dose-response analysis performed on these two studies by means of BMD modelling resulted in a BMDL10 of 26 µg/kg bw per

day and a NOAEL of 50 µg/kg bw per day, respectively.

12. Applying a probabilistic uncertainty approach (WHO ICPS/APROBA), the BfR considered that the TDI derivation and uncertainty analysis were not separated but rather the TDI was determined as the result of the uncertainty analysis in an integrated way. In contrast to EFSA, the BfR did not apply a single HEDF value to the derivation of the TDI within the uncertainty analysis but applied the 5^{th} and 95^{th} percentile and median HEDFs., together with typical uncertainties, e.g. interhuman variability, study duration.

13. Due to the conservatism in the assessment the BfR considered the resulting TDI of 0.2 µg/kg bw per day to be protective of 99% of the population, with 95% confidence. The TDI would also be protective for any other relevant effects/toxicological endpoints, including a 100% increase in the respective intermediate endpoints.

COT View

14. 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.

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

16. 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 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.

17. The use of a male reproductive endpoint, i.e. sperm count and mobility by the BfR was consistent with the critical endpoint used in previous COT assessments. While the COT agreed that the BfR added a significant level of conservatism to their derivation of the TDI, their overall assessment avoided overall conservatism.

18. 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. Both, the BfR and the COT agreed with the uncertainties in this approach, hence the BfR did not undertake an exposure assessment in their evaluation **and the COT stressed the importance of updated occurrence levels to fully assess any potential risks to consumers.**

Conclusions and Next Steps

19. 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.

20. The COT considered the endpoint and approach applied by the BfR to be more reasonable than EFSA's assessment, albeit still with a significant level of conservatism.

21. The COT acknowledges that given the size of the database, undertaking their own weight of evidence approach, with a transparent data integration, would not be a short undertaking. Hence, after assessment of the scientific evidence and approaches taken to establish a health based guidance value, the Committee agreed to adopt the TDI of 0.2 ug/kg bw per day derived by the BfR.

22. The Committee will be publishing a supplementary statement in due course, providing detail on their discussions of the EFSA opinion and BfR assessment, their evaluation of the evidence base, and deliberations to adopt the TDI derived by the BfR.

23. In line with EFSA and the BfR, the Committee highlighted that the most current exposure data predates the 2015 EFSA opinion. **To undertake a full risk assessment, and to fully assess realistic exposures in and potential risks to the UK population, up to date exposure data will be required.**

COT position paper

February 2024