Position papers

Position paper on bisphenol A

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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 German Federal Institute for Risk Assessment (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. Where it is permitted, operators must ensure that BPA 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) per day was based on increased mean relative kidney weight observed in animal studies and employed a human equivalent dose (HED). Based on their exposure assessment in 2015, 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 (EC) 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 had become available since the last assessment and should seek to clarify the remaining

uncertainties concerning the toxicological endpoints of BPA.

5. 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 BfR were discussed at the May 2023 meeting.

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

2023 EFSA evaluation

7. 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 target of BPA. An increase in the percentage of Th17 cells, a type of white blood cell, was reported in mice treated with BPA. The reported increase in these cells, which play a pivotal role in immune responses and are involved in inflammatory conditions, was considered as the most sensitive endpoint and hence the critical effect of BPA. While EFSA agreed that no direct causal link between the observed increase in Th17 cells and an inflammatory response has been established, they noted that there is evidence of a link between changes in the number of Th17 cells (an intermediate endpoint, i.e. not the final toxic effect) and adverse outcomes, as Th17 cells are involved in a number of diseases with inflammatory pathogenesis, e.g. psoriasis, asthma.

8. EFSA’s new tolerable daily intake (TDI) of 0.2 ng BPA/kg bodyweight per day was based on a human equivalent dose (HED) of 8.2 ng/kg bw per day, converted from the lower confidence level of the benchmark dose (BMDL40) for a 40% increase in the percentage of Th17 cells in mice. The benchmark response was selected on the basis of the variance observed in the numbers of Th17 cells in a healthy human population. EFSA applied an overall uncertainty factor (UF) of 50, using the default UFs of 2.5 and 10 for interspecies toxicodynamic differences and intraspecies variability in toxicokinetics and toxicodynamics, respectively. No UF was applied for interspecies 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.

9. Although this new TDI is higher than the value of 0.04 ng/kg bw proposed in their draft opinion, based on the exposures estimated by EFSA in 2015, mainly from data from 2008 – 2012, mean and high-level consumers of all age groups could potentially exceed the new TDI by 2-3 orders of magnitude.

10. 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 were obliged to present joint documents to the European Commission delineating the contentious scientific issues and identifying relevant uncertainties in the data.

2023 BfR assessment

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

12. A comprehensive systematic literature review was undertaken. The reliability of the studies was assessed based on pre-defined criteria 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 assessment were 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.

13. The BfR considered the immunological studies to be inconsistent regarding effects size and dose response, as well as suffering from shortcomings in design and reporting. Given that the increase in Th17 cells represents only an intermediate endpoint, for which a causal link to apical effects in a dose range relevant to humans is unclear, the BfR considered 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 (i.e. decreased sperm count and mobility, sperm viability, sperm morphology, changes to testis histology and weight) as the most sensitive endpoint and based its TDI derivation on reduced sperm count observed in two studies in rats. Dose-response analysis performed on these two studies by means of BMD modelling

yielded a BMDL10 of 26 µg/kg bw per day for the first study, but data from the second did not meet the BfR's criteria for BMD modelling, and so a NOAEL of 50 µg/kg bw per day was identified.

14. EFSA applied a deterministic uncertainty approach, deriving single point uncertainty estimates, combining multiple assumptions and applying them to the point of departure (PoD) to derive the TDI. The BfR applied a probabilistic uncertainty approach (WHO IPCS/APROBA), using a range of probabilistic distributions, considering uncertainty in both directions, such that the value could be increased or decreased, thereby integrating the uncertainty analysis and derivation of the TDI. In contrast to EFSA, the BfR did not apply a single HED factor in the derivation of the TDI within the uncertainty analysis but applied the 5th and 95th percentile and median HED factors, together with typical uncertainties, e.g. interhuman variability, study duration.

15. 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 intermediate endpoints. If BPA did cause any adverse immunological effects in humans, the BfR considered it unlikely this would be at exposures in the range of the TDI.

COT view

16. 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.

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

18. 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 not only in the evaluation for the relevant endpoint selection but also in 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 utilised in 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.

19. 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 had added a significant degree of conservatism to their derivation of the TDI, their overall assessment had avoided unnecessary conservatism.

20. EFSA (2015) previously compared their temporary TDI (t-TDI) with exposure estimated at that time, and concluded that there was no health concern for any age group from dietary exposure and low health concern from aggregate exposure to BPA. In their most recent opinion, EFSA was not explicitly asked to perform an exposure assessment and hence used the exposures estimated in 2015, noting that the data used may not accurately reflect the current (i.e. 2023) exposures of consumers. Both, the BfR and the COT agreed with the uncertainties inherent in this approach, but the BfR did not undertake an exposure assessment in their evaluation and both the BfR and the COT stressed the importance of updated occurrence levels to fully assess any potential risks to consumers.

Conclusions and next steps

21. The Committee considered the new evidence available on BPA since its last review, and while it is possible that the TDI would need to be revised to account for this new evidence, 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 intermediate endpoint selected in EFSA's assessment as the basis of their TDI.

22. The COT acknowledged that given the size of the database, undertaking a risk assessment on BPA, with a weight of evidence approach and transparent data integration, would not be a short undertaking. To ensure timely assurance of consumer protection, the Committee therefore also considered the assessment undertaken by the BfR in 2023 and concluded that the endpoint selected and

approach applied by the BfR were more scientifically robust and appropriate than those used by EFSA. Therefore, the Committee agreed to adopt the TDI of 0.2 ug/kg bw per day derived by the BfR.

23. The Committee could not any identify any endpoint that would be a more suitable basis of the TDI. 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.

24. In line with EFSA and the BfR, the Committee highlighted that the most recent exposure data available predates the 2015 EFSA opinion. To be able to u ndertake a full risk assessment, the COT will require up to date exposure data, which will enable the Committee to fully assess realistic exposures in, and potential risks to, the UK population.

COT position paper

May 2024