Evaluations by Regulatory bodies since the EFSA 2023 Opinion

In this guide

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

15. During the public consultation on the new EFSA opinion in 2021/2022, both, the European Medical Agency (EMA) and the German Federal Institute for Risk Assessment (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.

16. As the diverging views could not be resolved, according to the founding regulation, EFSA (Article 30 of Regulation (EC) No 178/2002) and the EMA (Article 59 of Regulation (EC) No 726/2004) and BfR were obliged to present

joint documents to the EC clarifying their scientific issues and identifying relevant uncertainties in the data. These documents are publicly available (EFSA/EMA, 2023; EFSA/BfR, 2023).

European Medical Agency (EMA)

17. The EMA did not agree with EFSA's revised TDI due to the two agencies different scientific approaches to risk assessment and methodology for quantifying risk, i.e. the adverse effect definition, the intermediate versus apical endpoint (final observable), the approach applied for consideration of studies and the risk assessment approach including the clinical relevance/extrapolation from animal studies for use in humans.

18. EFSA and the EMA had diverging views on what could be considered sufficient scientific evidence to demonstrate that an intermediate endpoint in animals was causally associated with an adverse effect in humans. Furthermore, both agencies disagreed on the method for quantifying the risk and establishing an exposure level considered safe in humans.

German Federal Institute for Risk Assessment (BfR)

19. Both, EFSA and the BfR acknowledged that the interpretation of available information and risk assessment were linked to the tools and methodologies applied, resulting in their divergence of opinion. The key points of divergence were the adverse effect definition, the inclusion/exclusion of scientific information, apical versus intermediate endpoint (reference point acceptability, adversity, relevance), reproductive toxicity endpoints, uncertainty analysis and choice of HED factor (HEDF).

20. Due to their divergence with EFSA's assessment, the BfR did not support the new TDI set by EFSA and published their own assessment of BPA in 2023. The assessment provided a re-evaluation of the critical endpoints identified by EFSA (2023) and an independently derived TDI.

21. The BfR undertook a literature review, and the reliability of the studies was assessed based on pre-defined criteria and grouped into three tiers reflecting the respective 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 available on these endpoints from the EFSA 2015 and 2023 assessments.

22. The BfR considered the immunological studies to be inconsistent regarding effect size and dose response, as well as suffering from shortcomings in design and reporting. Given that the increase in Th17 cells represented only an intermediate endpoint, for which a causal link to apical effects in a dose range relevant to humans was unclear, the BfR considered immunological effects in humans, if they occurred, 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 motility, 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 (Liu et al., 2013; Srivastava and Gupta, 2018). Dose-response analysis performed on these two studies by BMD modelling resulted in a BMDL10 of 26 µg/kg bw per day for one study (Liu et al., 2013), and a no observed adverse effect level (NOAEL) of 50 µg/kg bw per day for the other study (Srivastava and Gupta, 2018); data from the second study did not meet the BfR's criteria for BMD modelling.

23. 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 HEDF in the derivation of the TDI within the uncertainty analysis but applied the 5^{th} and 95^{th} percentile and median HED factors, together with typical uncertainties, e.g. interhuman variability, study duration.

24. Due to the conservatism in their 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. Should BPA cause any adverse immunological effects in humans, the BfR considered it unlikely this would be at exposures in the range of the TDI.

United States Food and Drug Administration (FDA)

25. In 2024, following the publication of both EFSA's and the BfR's evaluations of BPA, the United States Food and Drug Administration (US FDA) considered whether there was a need to change their position on the risk from BPA.

26. The US FDA assessed four studies in their evaluation, three were recent studies, and one had been previously evaluated. Of those four studies, two studies (Camacho et al., 2019; Dere et al., 2018) were negative for sperm effects, while the other two studies (Srivastava and Gupta, 2018; Liu et al., 2013, Part I and II) showed adverse effects on sperm parameters. The US FDA considered the negative studies methodologically strong with consistent findings, while the findings from the two positive studies were not easily comparable (FDA, 2024; unpublished).

27. Overall, the US FDA did not consider there to be any new evidence that would indicate an elevated concern regarding the effects of BPA on sperm parameters or testicular toxicity and therefore saw no need to change their previous conclusions on the safety of BPA. The US FDA therefore maintained a NOAEL of 5 mg/kg based on oral dosing studies for risk or safety assessments (FDA, 2014).

28. The US FDA noted that adverse effects occurred at concentrations of BPA that were well above established exposure levels in humans (FDA, 2024; unpublished).