Evaluations prior to the 2023 EFSA Opinion

In this guide

In this guide

1. Annex A TOX/2025/47 - Introduction
2. Annex A TOX/2025/47 - Evaluations prior to the 2023 EFSA Opinion
3. Annex A TOX/2025/47 - Evaluations by Regulatory bodies since the EFSA 2023 Opinion
4. Annex A TOX/2025/47 - COT review of BPA
5. Annex A TOX/2025/47 - Overall conclusion by the COT
6. Annex A TOX/2025/47 - COT Evaluation Timeline
7. Annex A TOX/2025/47 - Abbreviations
8. TOX/2025/47 Annex A - References
9. TOX/2025/47 Annex A - Literature search on the reproductive toxicity, immunotoxicity, pathology and histopathology of BPA

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

EFSA

4. In 2015, EFSA assessed the risk to public health from exposure to BPA using a weight of evidence (WoE) approach and considered reproductive and developmental effects, neurological and neurodevelopmental effects, immune effects and cardiovascular and metabolic effects “as likely as not” but considered it “unlikely” for BPA to be carcinogenic or mutagenic. Adverse effects on the kidney and mammary gland were considered “likely” and subject to benchmark dose (BMD) modelling. EFSA calculated a lower confidence level of the BMD (BMDL10) of 8,960 µg/kg bw per day for changes in mean relative kidney weight in a two-generation toxicity study in mice, however no BMDL10 could be calculated for mammary gland effects. Based on the available data on

toxicokinetics, the BMDL10 was then converted to a human equivalent dose (HED) of 609 µg/kg bw per day. EFSA applied a total uncertainty factor (UF) of 150 (2.5 for interspecies differences (2.5 for toxicodynamics and 1 for toxicokinetics as toxicokinetic differences have been addressed in the HED approach),10 for intraspecies differences, and an extra factor of 6 to account for the uncertainties in the database; 2.5 x 10 x 6) to the HED to derive a t-TDI of 4 µg/kg bw per day.

5. Based on estimated exposures, EFSA concluded there was no health concern for any age group from dietary exposure to BPA and a low health concern from aggregated exposure, i.e. exposure to BPA from all sources. EFSA however noted there was considerable uncertainty in the exposure estimates for non-dietary sources.

Dutch National Institute for Public Health and the Environment (RIVM)

6. In 2014, the Dutch National Institute for Public Health and the Environment (RIVM) published a report, providing an overview of the current state of knowledge on BPA (Part 1).

7. In 2016, the RIVM published recommendations for risk management (Part 2) evaluating the scientific knowledge and assessing possible health risks. The RIVM concluded that based on the current health hazard and information on exposure there was no health concern for BPA at the levels of dietary exposure estimated by EFSA in 2015 and low concern on aggregate exposure. A risk among neonates in intensive care units and foetuses of pregnant workers through dermal exposure could not be excluded. In addition, a risk among general workers involved with BPA manufacture as well as skin sensitisation of workers in industry processes working with BPA could not be excluded.

8. The RIVM also considered immunological data published by Menard et al. (2014a, b) which suggested that BPA could lead to the development of food allergies and have adverse effects on resistance to infections at exposures lower than the current European standards, i.e. the occupational exposure limit (OEL), t-TDI and dermal derived no effect level (DNEL). Neonates, infants and young children appeared to be more susceptible. Following the same approach as EFSA in 2015 to derive a t-TDI, the RIVM highlighted that the effects were observed in animals at a HED potentially a factor of 10 lower than the HED on which EFSA based its t-TDI on. The RIVM therefore concluded that the new study warranted reconsideration of the current standards and recommended that the Dutch

Government file a request to EFSA to revisit the t-TDI, to the EC to revisit the occupational exposure limit (OEL) and the derived no effect levels (DNELs) and to the European Chemicals Agency (ECHA) to re-open the evaluation of the health hazard of BPA.

9. The RIVM considered that the risk may be reduced through substitution of BPA with alternatives and included a number of alternatives in its report. They did however acknowledge that for most of these alternatives, toxicological characterisation was lacking.

Opinion of the EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (CEP), 2023

10. In 2016, the EC mandated EFSA to re-evaluate the risk to public health related to the presence of BPA in foodstuffs and establish a TDI. 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, following a pre-established protocol, and any new evidence since their last evaluation in 2015.

11. EFSA identified the immune system as the most sensitive target of BPA based on an increase in the percentage of Th17 cells reported in female mice treated with BPA via drinking water from gestational day (GD) 0 to postnatal day (PND) 21. Th17 cells are a subset of pro-inflammatory T helper cells which play a pivotal role in immune responses and are involved in inflammatory conditions. 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 was 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.

12. EFSA’s new TDI of 0.2 ng BPA/kg bw per day was based on a HED of 8.2 ng/kg bw per day, converted from the BMDL40 for a 40 % increase in the percentage of Th17 cells in mice. The benchmark response (BMR) was selected on the basis of the variance observed in the numbers of Th17 cells in a healthy human population. EFSA applied an overall 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. The resulting value was rounded to 0.2 ng/kg bw per day.

13. In their uncertainty assessment, EFSA applied a deterministic approach, deriving single point uncertainty estimates, combining multiple assumptions and applying them to the point of departure (POD) to derive the TDI.

14. While EFSA did not undertake an exposure assessment, given that the available exposure data were from 2008 – 2012, comparison of exposure estimates from 2015 would imply that mean and high level consumers of all age groups could potentially exceed the new TDI by 2-3 orders of magnitude.