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

Supplementary statement to the COT's position paper on bisphenol A (BPA)

Introduction

1. Bisphenol A (BPA) is used as a monomer in the manufacture of polycarbonates (PC), epoxy resins and other polymeric materials, and certain paper products (thermal printing). BPA was prohibited in coatings and varnishes for food contact materials (FCMs) intended for infants and young children in September 2018. However, it continued to be used and authorised in the European Union (EU) and United Kingdom (UK) for applications such as reusable bottles, tableware and storage containers, thermal paper coatings and protective linings in food and beverage cans and vats. Where BPA was permitted at the time, operators had to ensure that BPA observed the specific migration limit (SML) of 0.05 mg/kg (EC (No) 2018/213). The SML set in the EU and UK was based on the European Food Safety Authority's (EFSA) 2015 evaluation of BPA and a Temporary Tolerable Daily Intake (t-TDI) of 4 µg/kg body weight (bw) per day.

2. In 2016, the European Commission (EC) mandated EFSA to re-evaluate the risk to public health related to the presence of BPA in foodstuffs. A new TDI of 0.2 ng BPA/kg bw per day was established in EFSA's final evaluation in 2023. Although this final TDI was higher than that proposed initially, mean and high level consumers of all age groups would exceed the new TDI by 2-3 orders of magnitude.

3. In December 2024, the EU adopted a ban on the use of BPA in FCMs. This took effect in January 2025, with an 18-month phase-out period for industry compliance. The ban means that BPA will no longer be allowed in products that come into contact with food or drink, e.g. coating of metal cans, reusable plastic bottles, water coolers and other kitchenware. The EU ban includes salts of BPA and, as a precautionary measure, other bisphenols and bisphenol derivatives due to shared characteristics with BPA, such as similarities in structure and activity (EC (No) 2024/3190). Some bisphenols, e.g. bisphenol S (BPS), have already been subject to harmonised classification and have been listed in Part 3 of Annex VI Regulation (EC) No 1272/2008, as they have demonstrated hazardous properties to human health, i.e. reproductive toxicity.

Evaluations prior to the 2023 EFSA Opinion

EFSA 2015

4. In 2015, EFSA assessed the risk to public health from exposure to BPA using a weight of evidence (WoE) approach. Reproductive and developmental effects, neurological and neurodevelopmental effects, immune effects and cardiovascular and metabolic effects were considered “as likely as not” but carcinogenicity and mutagenicity were considered “unlikely”. Adverse effects on the kidney and mammary gland were considered “likely” and subjected to benchmark dose (BMD) modelling. EFSA calculated a lower confidence level of the BMD ($BMDL_{10}$) 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 $BMDL_{10}$ could be calculated for mammary gland effects. Based on the available data on toxicokinetics, the $BMDL_{10}$ 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 x 10 x 6: 2.5 for interspecies differences (2.5 for toxicodynamics; and 1 for toxicokinetics as toxicokinetic differences were addressed in the HED approach),10 for intraspecies differences, and an extra factor of 6 to account for the uncertainties in the database) 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; however, considerable uncertainty in the exposure estimates for non-dietary sources was noted.

Dutch National Institute for Public Health and the Environment (RIVM), Part I 2014 and Part II 2016

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 scientific knowledge concerning BPA and assessing its 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 from all sources. A risk to fetuses of pregnant workers through dermal exposure and among

neonates in intensive care units could not be excluded. Occupational risks to general workers involved with BPA manufacture and 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 affect the human immune system. Both food allergies and adverse effects on resistance to infections were reported 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 used by EFSA in 2015 to derive a t-TDI, the RIVM highlighted that the effects were observed in animals at a dose that would result in a HED that would potentially be a factor of 10 lower than the HED used by EFSA as the basis of its t-TDI. 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 toxicological characterisation was lacking for most of these alternatives.

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 in order to establish a TDI. For the derivation of their new TDI, the EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (CEP) used a pre-established protocol to assess any new evidence from animal data and human observational studies from 2013-2021, previously not considered in their 2015 assessment. EFSA also undertook a targeted re-evaluation of some of the studies included in the WoE assessment that underpinned their 2015 Opinion.

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 has been established between the observed increase in Th17 cells and an inflammatory response, 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. The point of departure (POD) for EFSA's new TDI of 0.2 ng BPA/kg bw per day was a HED of 8.2 ng/kg bw per day, converted from the $BMDL_{40}$ for a 40 %

increase in the percentage of Th17 cells in mice. This benchmark response was selected on the basis of the variance observed in the numbers of Th17 cells in a healthy human population. Applying 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 because this was already accounted for in the conversion to the HED) and an additional UF of 2 based on the uncertainty analysis performed, EFSA applied an overall UF of 50. The resulting value was rounded to 0.2 ng/kg bw per day.

13. EFSA applied a deterministic approach to its uncertainty assessment, deriving single point uncertainty estimates, combining multiple assumptions and applying them to the POD to derive the TDI.

14. EFSA did not undertake a new exposure assessment, but used previous estimates based on data from 2008-2012. Comparison of exposure estimates from 2015 to the new TDI would imply that mean and high level consumers of all age groups might exceed the new TDI by 2-3 orders of magnitude.

Evaluations by Regulatory bodies since the EFSA 2023 Opinion

15. During the public consultation on the new EFSA opinion in 2021/2022, both the European Medicines Agency (EMA) and the German Federal Institute for Risk Assessment (BfR) provided comments highlighting their diverging views from EFSA 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. The diverging views could not be resolved so, according to the founding regulations, EFSA (Article 30 of Regulation (EC) No 178/2002), the EMA (Article 59 of Regulation (EC) No 726/2004) and BfR were obliged to present joint documents to the EC clarifying their scientific differences and identifying relevant uncertainties in the data (EFSA/EMA, 2023; EFSA/BfR, 2023).

European Medicines Agency (EMA), 2023

17. The EMA disagreed with EFSA's revised TDI as a consequence of to the two agencies' different scientific approaches to risk assessment and methodology for quantifying risk. Points of disagreement were the adverse effect definition, the use of an intermediate rather than an apical (final observable) endpoint, the approach applied for consideration of studies and the risk assessment approach, including clinical relevance and extrapolation from animal studies to 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, the 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), 2023

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

20. 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 in 2023 and presented an independently derived TDI.

21. The BfR undertook a literature evaluation and assessment limited to the critical endpoints identified by EFSA (reproductive toxicity, immunological effects, increased serum uric acid, and toxicokinetics) and considered new evidence together with the literature and data available on these endpoints from the EFSA 2015 and 2023 assessments. Study reliability was assessed based on pre-defined criteria and grouped into three tiers reflecting the respective WoE.

22. The BfR considered the immunological studies to suffer from shortcomings in design and reporting and to have inconsistencies regarding effect size and dose response. Given that the increase in Th17 cells in mice was 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 $BMDL_{10}$ 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 (Srivastava and Gupta, 2018; data from this 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, and 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 occur at exposures in the range of the TDI.

United States Food and Drug Administration (FDA), 2024

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 evaluated previously. Of the four studies, two (Camacho et al., 2019; Dere et al., 2018) were negative for sperm effects, while the other two (Srivastava and Gupta, 2018; Liu et al., 2013) 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 their NOAEL of 5 mg/kg bw/day based on oral dosing of rodents in two multigenerational studies for risk or safety assessments (FDA, 2008; 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).

29. The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) acknowledged the conclusion by the US FDA to maintain their

previous safety level but did not further consider the details of the US FDA evaluation in their assessment of BPA.

COT review of BPA

30. Following the publication and assessment of the new EFSA Opinion in 2023, the COT agreed that, while the TDI would need to be revised to account for new evidence, the WoE did not support the conclusions drawn by EFSA or a TDI as low as that derived by EFSA. In line with the EMA and BfR, the COT raised a number of concerns, highlighting a lack of transparency on how the evidence had been integrated by EFSA to derive the POD for the derivation of a HBGV and EFSA's use of a predetermined protocol which restricted the inclusion of studies and subsequent data evaluation to a specific time period. There was a wider data set available for BPA and this should have been considered by EFSA, not only in the evaluation for the relevant endpoint selection but also in the derivation of the HEDF.

31. The COT acknowledged that, given the size of the database, undertaking an independent risk assessment on BPA, with a WoE approach and transparent data integration, would be a lengthy undertaking and would not allow timely assurance of consumer protection in the UK. It therefore considered the WoE assessment by EFSA (2015, 2023) and the TDI established by the BfR (2023), as well as their methodological approaches, in order to derive a HBGV.

32. To ensure no relevant evidence had been published since the BfR conducted their assessment, a literature search was undertaken. This used an in-house search engine and retrieved publications from PubMed, Scopus, Ebsco (Food Science

Source) and Springer (see Annex A for search terms), focussing on any papers published between January 2022 and June 2024.

33. In line with EFSA (2015; 2023) and the BfR (2023), the COT concluded that toxicological endpoints other than those which resulted in immunological or reproductive effects occurred consistently at higher dose ranges; any HBGV based on either of these two endpoints would also be protective for other toxicological endpoints. The literature search therefore focused on the main endpoints of BPA, i.e. reproductive toxicity and immunotoxicity, but also included search strings for pathology and histopathology. Articles were excluded if they were general review articles, focused on other effects, were published prior to 2022 or focussed on biomonitoring (occurrence data) or detection methods of BPA.

34. While the COT acknowledged the diverging opinion by the EMA it was not further considered in the COT's assessment of BPA. The EMA raised scientific concerns about the endpoint applied by EFSA for the derivation of a HBGV. These aligned with the concerns highlighted by the COT, however the EMA's approach to risk assessment differs from that of the COT, in that it weighs patient benefit against risk.

35. The COT also considered assessments undertaken by other European or international authorities. While the Committee considered it useful to have seen the RIVM's assessment, specifically the second part, they noted that the report was published in 2016 and therefore addressed neither the selection of the critical endpoint nor the approach taken by EFSA in 2023. The report was published before

the EFSA 2023 assessment and would have fed into the new EFSA opinion, but it would not provide answers to the concerns raised by the COT. The US FDA published a technical review in 2024 based on four studies, all of which the COT noted were also discussed as part of the BfR assessment. The COT considered the technical review clear and scientifically robust; however, due to differences in weighing of evidence, the US FDA reached a different conclusion on these studies, confirming their previous position on BPA and seeing no need to change their current advice.

36. The COT acknowledged the list of alternatives provided by the RIVM, as well as any other considerations given to alternatives in the EU. However, assessing alternatives was outside the mandate of this activity of the COT.

Immune effects

37. In 2023, EFSA strengthened and updated their earlier evaluation of BPA and concluded that there was credible evidence that BPA adversely affects the immune system, notable cellular immunity (i.e. increases in serum and tissue levels of interleukin (IL) 17, and production of IL-17 by stimulated spleen cells, together with an increased percentage of Th17 cells) and other parameters indicating allergic lung inflammation (i.e., increased serum immunoglobulin E (IgE), increased bronchoalveolar lavage fluid (BALF) eosinophils and neutrophils and neutrophil-mediated inflammation of the epididymis). Based on a WoE approach and BMD analysis, EFSA concluded that the increase in percentage of Th17 cells, which are involved in immune and inflammatory responses, was the most sensitive endpoint and hence the critical effect for BPA exposure.

38. Following their WoE evaluation the BfR (2023) concluded that the available data showed consistent immunotoxic effects of BPA, noting the same endpoints EFSA had identified. However, there was a lack of standardization in the literature for immunotoxicity endpoints, and while intermediate endpoints were regularly investigated, results on adverse apical outcomes were less well defined. In addition, effects on IL-17 had not yet been demonstrated in species other than the mouse.

39. Looking at the body of evidence, the COT acknowledged that there was clear evidence for BPA causing inflammation and an increase in the percentage of Th17 cells. In agreement with the BfR, the COT noted that similar intermediate endpoints were addressed across several studies under similar testing conditions. The available studies addressed gestational and neonatal exposure in male and female mice; only one study (Ogo et al., 2018) used male rats. In the studies considered by COT, animals were exposed to BPA at concentrations ranging from 0.0075 µg/kg bw per day to 50 mg/kg bw per day. Depending on the study and endpoint, animals were exposed either on GD0 or from GD0 to PND21 and effects were generally observed around PND21 or, in some cases, at PNDs between 40 to 50. Only a few studies considered exposures into adulthood (approximately PND50; Gao et al. 2020) or analysis as late as PND170 (Malaise et al., 2017a). The adverse effects of BPA were comparable across exposure concentrations and durations, significant effects being reported at BPA exposures of approximately 5-50 µg/kg bw per day (Luo et al., 2016; Dong et al., 2023; Gao et al., 2020; Wang et al., 2020).

40. In general, exposure of mice and their offspring to BPA resulted in increased interferon gamma (IFN-ɣ) (in the colon, lamina propria and mesenteric lymph nodes (MLN)), Th1 cells (in the spleen) and Th17 cells (in the lamina propria, MLN and spleen) and a decrease in lysosome activity (intestine), immunoglobulin A (IgA) concentration (in faecal samples), IgA plasma cells (in the lamina propria), IgA cells (in the colon), activated T cells (in the lamina propria), Th cells (in MLN), and Treg cells (in the lamina propria, spleen, MLN) and alterations in dendritic cell subsets. Increases in IL-6, 17, 21 and 23 concentrations were observed in the serum together with increases in IL-6 and neutrophilia in the epididymis. In addition, changes in anti-ovalbumin IgE concentrations in serum and altered production of IL-4, IL-13, tumour necrosis factor alpha and IFN-ɣ in splenocytes were reported. Studies also reported changes in the proportions of macrophages, lymphocytes, eosinophils and neutrophils and the up- or downregulation of genes associated with inflammation (Bodin et al., 2014; O'Brian et al., 2014; Luo et al., 2016; Malaise et al., 2017b; Ye et al., 2023; Gu et al., 2024).

41. A study by Dong et al. (2023) suggested that exposure to BPA contributed to the development of systemic lupus erythematosus (SLE) in a susceptible MRL/lpr mouse model. Several other studies looking at BPA exposure and inflammatory responses have also used susceptible (animal) models for inflammation. It is unclear whether the development of SLE in the susceptible mouse strain or reduced lung function in murine asthma models should be considered true apical endpoints. The transferability of these results to humans is unclear, disease models in mice not being representative of the human situation. In addition, not all studies assessing immunological endpoints were conducted to the Organisation for Economic Co-

operation and Development (OECD) guidelines or Good Laboratory Practice (GLP) standards. Hence, the COT considered that, while these studies added to the overall body of evidence, they had a number of limitations, and it was unclear whether they demonstrated a true effect of BPA.

42. Th17 cells are well established as an indicator/marker for inflammation, however, because inflammation is driven by numerous factors, it is unclear how an apical endpoint based on changes in Th17 cells would manifest. To date no studies have demonstrated progression from such an intermediate endpoint, i.e. an increase of Th17 cells, to an apical effect, i.e. an inflammatory response/effect, at a concentration of BPA relevant to human exposure. In addition, no adverse outcome pathway linking BPA exposure to an adverse immunological endpoint has been established.

43. In general, the COT queried whether an intermediate endpoint would be sufficiently robust to derive a HBGV; specifically, they did not agree with EFSA that an increase in percentage of Th17 cells was a scientifically relevant and robust intermediate endpoint to be utilised in the derivation of a new HBGV for BPA. After weighing the available data, the COT concluded that appropriate evidence that the change in Th17 cells consistently led to adverse immune effects or inflammatory response in humans was lacking. Immunological effects, therefore, were not scientifically justifiable to predict the adverse health effects of BPA. Given the uncertainties over the endpoint, a more robust WoE approach and evidence integration should be applied to a wider dataset to derive a more reliable and relevant endpoint on which to base the HBGV.

Reproductive effects

44. In 2015, EFSA concluded, based on evidence available at the time, that BPA caused adverse effects on reproduction; however, the effects were highly variable over a wide range of doses. In 2023, EFSA concluded once more that BPA adversely affected development and male and female reproduction in experimental animals, i.e. an adverse effect was “likely”. In line with their previous assessment, however, EFSA considered the available human data not sufficient to establish a causal relationship between BPA exposure and developmental and/or reproductive effects in humans.

45. The BfR, in 2023, acknowledged that the variability in the data, including new evidence, continued to be considerable; however, they nonetheless deemed the scientific evidence sufficient to consider effects on male reproduction the key adverse effect of BPA. This was based on a WoE approach, focussing on the most likely endpoints, as identified by EFSA (2023), i.e. sperm motility, testis and epididymis histology. The BfR based its TDI derivation on reduced sperm count observed in two studies in rats. Liu et al. (2013) exposed 9 week old male Wistar rats to BPA at 2, 20 or 200 µg/kg bw per day via gavage for 60 days and reported significant effects on sperm count at 200 µg/kg bw per day. Srivastava and Gupta (2018) exposed adult male Wistar albino rats to BPA at 5, 50 and 100 µg/100g bw per day (50, 500 and 1000 µg/kg bw per day) for 90 days. Results demonstrated significant effects on sperm count at 500 µg/kg bw per day and a dose-dependent decrease in testis weight at 500 and 1000 µg/kg bw per day. No effects were reported at 50 µg/kg bw per day.

46. The COT critically appraised both EFSA's and the BfR's WoE approach and agreed with the BfR's selection of the key endpoint, i.e. male reproduction. However, to ensure all relevant information had been evaluated, the COT also considered evidence on reproduction published since the BfR's assessment. In line with the WoE approached used by the BfR and to ensure the appropriate endpoints were reviewed, the new evidence was categorised using the three stages of the developmental and reproductive process and separated into studies of male and female biology (Figure 1).

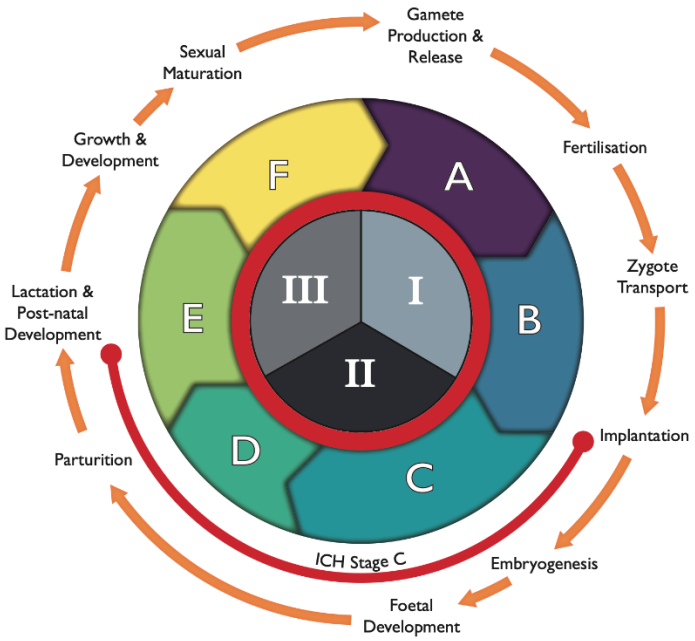

Figure 1: The reproductive and developmental process, adapted from IPCS (2001) and Spielmann (2009). The graph also includes the testing strategy by the FDA (1966; ICH, S5(R3), 2021), i.e. segments I (fertility), II (embryotoxicity/teratogenicity) and III (peri-post-natal toxicity), and stages A (pre-mating conception), B (conception to implementation), C (implementation to closure of the hard palate), D (closure of

hard palate to end of pregnancy), E (birth to weaning) and F (weaning to sexual maturity). Stage C spans both segment II and III, as indicated by the orange line.

47. The 70 new studies on reproductive endpoints were predominantly mechanistic and/or *in vitro*. While these were supportive in providing information on the mode of action over relatively consistent dose ranges, they did not provide any new knowledge on the mode of action of BPA on reproductive effects.

48. While several of the *in vivo* studies focussed on interventions to ameliorate effects of BPA with various substances (including natural products), studies by Molangiri et al. (2022) and Sturm et al. (2022) assessed male reproductive endpoints after gestational exposure to BPA at 0.4-40 µg/kg bw per day and 25 µg/kg bw, respectively.

49. Molangiri et al. (2022) reported effects on male reproduction, including high plasma testosterone, thickened membranes in the testis and reduced sperm motility via impaired phosphatidylinositol 3-kinase-protein kinase B (PI3K-AKT) signalling and increased expression of testes-expressed gene 11 (TEX11). The study suggested a window of susceptibility *in utero* that could have long lasting effects on male reproduction.

50. In contrast, the study by Sturm et al. (2022) did not report any reproductive effects. While minor changes were observed in testicular tissues, i.e. lower epithelial height of seminiferous tubules, this change did not have an impact on the apical endpoint. The BPA doses administered in this study were comparable to doses

reported in other studies as lowest observed adverse effect level (LOAEL) and NOEAL and the study therefore adds to the database and strengthens the evidence base related to observations relating to NOAEL/LOAEL.

51. Recent epidemiological studies on BPA were limited. Two biomonitoring studies provided further evidence of human exposure to BPA and potential risks to the population; however, data on reproductive or fertility endpoints were lacking (Hwang et al., 2023; Holmboe et al., 2022). A cross-sectional study by Jeseta et al. (2024) in 385 males (17-62 years of age; 2019 - 2021) provided a good assessment of BPA in male semen samples. The results indicated a significant correlation between exposure to BPA and decreased sperm motility and altered morphology but not traditional markers of sperm health such as sperm concentration, volume and total sperm count, and integrity of spermatozoa deoxyribonucleic acid (DNA) and BPA exposure.

52. Recent experimental data from rodent studies on the adverse effects of BPA on the female reproductive system reported effects on oocyte and ovarian weight as well as changes to reproductive hormones, ovarian follicles and ovarian development in F1 generation of exposed dams (Ozkemahli et al., 2022; Gonzalez-Gomez et al., 2023; Teteau et al., 2023). The data also showed gene changes *in vivo* (Gonzalez-Gomez et al., 2023) and *in vitro* (Teteau et al., 2023). In a recent correlation study (2020-2021) assessing BPA exposure and ovarian function and oocyte reserve in 111 women from a fertility clinic in North China no evidence of causation could be established (Zhang et al., 2023). While the study in humans by Zhang et al. (2023) did not look at pregnancy effects of BPA and thus does not allow

for a direct comparison to the animal studies noted above, it is the only available study done in humans at scale and therefore adds to the overall database.

53. Generally, effects on the female reproductive system were observed at doses several orders of magnitude higher than the POD used by both EFSA and the BfR. Hence, effects on the female reproductive system were not considered further by the COT, which agreed with the BfR that a HBGV based on male reproductive effects would also be protective for effects on the female reproductive system.

54. Weighing all the available evidence, the COT agreed with the BfR's assessment that the adverse effect of BPA on male reproduction was the critical endpoint and should be carried forward for the derivation of a HBGV. Data published since the BfR's assessment, while informative and adding to the overall database of BPA, did not provide any information to change the COT's current view.

Other toxicological endpoints

55. In 2023, EFSA followed a predefined protocol to identify evidence that had become available since their 2015 evaluation; this included the evaluation of some evidence not considered in their earlier assessment (EFSA, 2015). In addition to immunotoxicity and reproductive toxicity, EFSA considered carcinogenicity, genotoxicity, hepatotoxicity, renal toxicity, cardiotoxicity, neurotoxicity and developmental neurotoxicity, as well as effects on body weight, the lung, thyroid, parathyroid, pituitary and adrenal glands, the mammary gland, bone marrow, and haematological and metabolic effects.

56. Using the 2015 EFSA opinion as a starting point, the BfR conducted a targeted systematic literature review to retrieve evidence on the reproductive and immunotoxic effects of BPA that had become available since 2013. Having criticised the factor EFSA used to extrapolate from the critical dose in rodents to humans, the BfR also sought and considered new information on the toxicokinetics of BPA. The review also considered metabolic effects, however the available studies on increased serum uric acid were not considered suitable for a quantitative hazard assessment. The BfR noted that there remained uncertainty over this endpoint and more data would be required. Other endpoints, e.g. effects on the liver or kidney, were not included in the review because EFSA (2015; 2023) and ECHA (2014) had consistently reported the absence of adverse effects in the dose range of interest (≤ 4 μg/kg bw per day for humans). The BfR agreed with this conclusion and with EFSA's conclusion that it is "unlikely to very unlikely" that BPA presents a genotoxic hazard or demonstrates tumorigenic activity.

57. The COT agreed with EFSA and the BfR that the literature on BPA did not demonstrate genotoxic or carcinogenic potential and that adverse effects other than immunotoxicity or reproductive effects occurred at higher concentrations and were therefore not of direct relevance to the establishment of a TDI. The targeted literature search (non-systematic) conducted by the COT in 2024 therefore sought to identify publications on the potential immunotoxic or reproductive effects of BPA published since the literature search conducted by the BfR. For completeness, a literature search for pathology/histopathology was also included. Although the search terms were quite narrow a number of the papers retrieved covered BPA more broadly or considered the general toxicity of BPA.

58. Two of the papers retrieved did not include primary data. Prueitte and Goodmann (2024) was a critique of the EFSA assessment and their use of an intermediate immunotoxicity endpoint that had not been observed in species other than mice. The authors concluded that EFSA's new TDI was not supported by the totality of the available database on BPA but indicated that the t-TDI established by EFSA in 2015 would continue to be protective of human health. Kortenkamp et al. (2022) conducted a systematic review of BPA exposure and decline in semen quality. The authors were critical of both the EFSA and BfR assessment, stating that neither authority assessed the evidence on reproductive effects accurately. The COT noted that Kortenkamp et al. (2022) focussed on reproductive endpoints only and did not include considerations on immunotoxicity or the wider potential effects of BPA. The COT reviewed the information within the paper and highlighted that the papers cited by Kortenkamp et al. (2022) to underpin their interpretation of the evidence would have been available to EFSA and the BfR at the time.

59. The COT concluded that the new evidence on general toxicity, pathology/histopathology and included in the reviews/critiques highlighted above was not sufficient to alter the Committee's current alignment with the BfR.

Considerations on the point of departure

60. EFSA (2023) identified a $BMDL_{40}$ of 0.53 µg/kg bw per day as a POD for its derivation of a HBGV. This was based on the study by Luo et al. (2016) in which pregnant mice were exposed to BPA concentrations equivalent to 0.475, 4.75 and 47.5 µg/kg bw/day. The BfR (2023) derived a $BMDL_{10}$ of 26 µg/kg bw per day based

on a dose range of 2-200 µg/kg bw per day (Liu et al., 2013) and a NOAEL of 50 µg/kg bw per day based on a dose range of 50-1000 µg/kg bw per day (Srivastava and Gupta, 2018) as their POD.

61. Apart from the studies by Molangiri et al. (2022) and Darmani and Alkhatib (2024), the dose ranges or PODs in the studies identified in the recent literature search were orders of magnitude higher than the PODs used by EFSA and the BfR. Molangiri et al. (2022) exposed rats to BPA at a dose of 0.4 µg/kg bw per day, which was slightly lower than the BMDL derived by EFSA in 2023 and approximately 100-fold lower than the POD chosen by the BfR. The authors reported significant effects including increased weight in male offspring, a significant reduction in the expression of estrogen-related receptor gamma (ERRɣ) and changes in gene expression. Testicular morphology showed changes such as disoriented arrangement of seminiferous tubules, irregular-shaped Leydig cells, and a smaller number of mature sperms in lumens. Darmani and Alkhatib (2024) reported changes to serum hormone levels after exposure to BPA dimethacrylate (DMA) at a dose of 10 µg/kg bw per day. This is lower than the POD chosen by the BfR but 20-fold higher than the $BMDL_{40}$ selected by EFSA.

62. Although the effects reported in the study by Darmani and Alkhatib (2024) occurred at a dose lower than the POD established by the BfR, they were based on BPA-DMA, rather than BPA itself. Hence, while these provide an indication of adverse effects, it is not clear whether the effects seen with BPA-DMA are consistent with effects of BPA seen at the same dose. The effect dose was still higher than the POD applied by EFSA. The results by Molangiri et al. (2022) were in line with

previous studies, demonstrating adverse effects on male offspring after *in utero* exposure, albeit at lower levels, but the main focus of the study was BPS. Additional data would be required to fully establish whether the reported effects could be consistently seen at the reported dose levels.

63. While both studies contributed to the overall knowledge base, the COT did not consider this new evidence sufficient to reconsider their current alignment with the BfR or to suggest that the TDI would not be sufficiently protective of adverse effects of BPA.

Establishment of the TDI

64. Both EFSA and the BfR acknowledged that the interpretation of the available evidence and divergence in the risk assessment were linked to the tools and methodologies applied. The key points of divergence were the adverse effect definition, the inclusion/exclusion of scientific information, the use of an apical versus intermediate endpoint, uncertainty analysis and the HEDF.

65. To derive the POD for the derivation of the HBGV the BfR undertook BMD modelling on all suitable studies. While the effects on male reproduction were considered the critical endpoint, BMD modelling of immunotoxicological studies was also undertaken to evaluate to what extent the HBGV would also be protective for immunological effects. Weighing all the evidence, the BfR based their derivation of the TDI on the effect dose for reduced sperm count in two sub-chronic studies in rats (Liu et al., 2013; Srivastava and Gupta, 2018). Studies where the NOAEL was the highest dose tested were excluded from further assessment because it was unclear

at which dose, if any, a benchmark response would have been reached. The two selected studies were submitted to a probabilistic uncertainty assessment according to the approach by the World Health Organisation (WHO IPCS, 2017). In contrast to EFSA's deterministic approach, the distribution of possible HEDs resulting from toxicokinetic data were thereby combined with typical distributions for other uncertainties.

66. Both EFSA and the BfR extrapolated the POD to the TDI by substituting the toxicokinetic standard subfactor for interspecies extrapolation by a BPA-specific HEDF. The COT noted that both authorities applied the same human data but used different animal studies, resulting in HED values that differed by two orders of magnitude. This, together with the different approaches to the derivation of the TDI (deterministic versus probabilistic), led to a difference of three orders of magnitude in the resulting HBGVs. The approach taken by the BfR comprised a significant degree of conservatism in the derivation of the TDI; however, the COT deemed the overall assessment to have avoided unnecessary conservatism.

67. While the COT acknowledged that there was clear evidence of BPA causing an effect on the immune system, the evidence as a whole was not strong enough to support immunotoxicity as the critical endpoint. However, the TDI derived by the BfR would still be protective of a significant increase in the respective intermediate endpoint, as well as protective with respect to other toxicological endpoints. Based on the current body of evidence, adverse immunological and other toxicological effects in humans were unlikely to result from exposures up to the TDI of 0.2 µg/kg bw per day.

Considerations on the exposures of UK consumers

68. In line with EFSA and the BfR, the COT highlighted that the most recent exposure data predated the 2015 EFSA opinion. A comparison of the 2015 t-TDI with exposure estimates in 2015 found no health concern for any age group from dietary exposure and low health concern (i.e. considered unlikely to cause adverse health effects) from aggregate exposure to BPA from all sources. While EFSA was not explicitly asked to perform an exposure assessment in their 2023 evaluation, the exposures estimated from 2015 would lead to exceedances of approximately 2-3 orders of magnitude compared to the 2023 TDI. However, EFSA noted that exposure data from 2015 may not accurately reflect the current exposure scenarios of consumers. The BfR and the COT agreed with the uncertainties in this approach. 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. The COT highlighted that having an up-to-date exposure assessment would further mitigate any potential risk by providing an up to date picture of the current UK exposures.

Overall conclusion by the COT

69. Following the publication of the most recent EFSA evaluation in 2023, the COT agreed that there was a requirement to assess the new evidence on BPA and adjust the current TDI as necessary. To ensure timely consumer protection, rather than undertaking a lengthy assessment, the COT instead assessed the weighing of evidence and approaches taken by both EFSA and the BfR. A targeted non-

systematic literature search was also undertaken to ensure no new data that would affect the conclusions had been published since the BfR assessment in 2023.

70. The COT agreed with EFSA and the BfR that most adverse effects of BPA occur at doses higher than those that cause immunological effects and affect reproductive function and are therefore not of direct relevance, i.e. a HBGV derived on either immunological effects or reproductive toxicity would also be protective for other toxicological effects. The COT further agreed that BPA does not demonstrate genotoxic or carcinogenic potential.

71. While the COT acknowledged that BPA had a clear effect on an intermediate immune system endpoint, the evidence was not sufficient to consider immunotoxicity as the key adverse effect. The available data were not sufficiently robust to demonstrate a clear progression from an intermediate endpoint to a consequent apical effect. The COT instead agreed with the BfR that adverse effects on male reproduction, i.e. sperm count and motility, were the critical endpoint and should be applied to derive a HBGV. This was in line with previous COT assessments.

72. The studies published since the BfR assessment were informative and added to the overall knowledge base, but did not contain sufficient evidence to alter the view of the COT regarding the critical endpoint or effect dose.

73. The COT considered the BfR's TDI highly, but not excessively, conservative. Having evaluated the available information, the COT considered the endpoint

selected and approach applied by the BfR scientifically robust and agreed to adopt the TDI of 0.2 µg/kg bw per day established by the BfR.

COT Evaluation Timeline

Discussion of the Draft EFSA Opinion (TOX/22/11-16)

Discussion of the EFSA 2023 Opinion (TOX/23/25); COT First draft interim position statement

TOX/23/45: Second draft interim position statement on bisphenol A

TOX/23/50: Third draft interim position statement on bisphenol A

TOX/23/61: Bisphenol A: The Dutch National Institute for Public Health and the Environment (RIVM), BPA Part 2

TOX/24/08: Fourth draft interim position paper on bisphenol A

TOX/24/13: Fifth Draft Interim Position Statement on Bisphenol A

TOX/24/19: Sixth draft interim position statement on bisphenol A

COT Position Paper on Bisphenol A (BPA)

COT supplementary statement

June 2026

Abbreviations

AKT	Protein kinase B
APROBA	Approximate probabilistic analysis (tool)
BMD	Benchmark dose
BALF	Bronchoalveolar lavage fluid
BMDL	Lower confidence level of the benchmark dose
BPA	Bisphenol A
BPS	Bisphenol S
bw	Bodyweight
DMA	Dimethacrylate
DNA	Deoxyribonucleic acid
DNELs	Derived no effect levels
ERRɣ	Estrogen-related receptor gamma
FCM	Food Contact Materials
GD	Gestational day
GLP	Good laboratory practise
HBGV	Health based guidance value
HED(F)	Human equivalent dose (factor)
IFN-ɣ	Interferon gamma
Ig	Immunoglobulin
IL	Interleukin
LOAEL	Lowest observed adverse effect level
MLN	Mesenteric lymph nodes
NOAEL	No observed adverse effect level

OEL	Occupational exposure limit
PC	Polycarbonates
PI3K	Phosphatidylinositol 3-kinase
PND	Postnatal day
POD	Point of departure
SLE	Systemic lupus erythematosus
SML	Specific migration limit
t-TDI	Temporary tolerable daily intake
UF	Uncertainty factor
WoE	Weight of evidence
BfR	German Federal Institute for Risk Assessment
COT	Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
EC	European Commission
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EFSA CEP Panel	EFSA's Panel on Food Contact Materials, Enzymes and Processing Aids
EMA	European Medicines Agency
EU	European Union
US FDA	United States Food and Drug Administration
ICH	International Council for Harmonisation
IPCS	International Programme on Chemical Safety

OECD	Organisation for Economic Co-operation and Development
RIVM	Dutch National Institute for Public Health and the Environment
UK	United Kingdom
WHO	World Health Organisation

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Annex A

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

Supplementary statement to the COT's position paper on bisphenol A (BPA)

Literature search on the reproductive toxicity, immunotoxicity, pathology and histopathology of BPA

1. A literature search was performed from January 2022 until June 2024 using the following search terms:

(Bisphenol A OR BPA) AND (reproduct* OR immunotox* OR patholog* OR histopatholog* OR Th17)

2. The search returned 761 articles, of which 3 were duplicates. After manual filtering (titles and abstracts) 101 articles remained

- Broader BPA studies (4)
- Immune effects of BPA (10)
- Reproductive effects of BPA (70)
- Pathology/histopathology (8)
- Other toxic effects (9)

Annex B

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

Supplementary statement to the COT's position paper on bisphenol A (BPA)

Table 1: Comparison of approaches taken and endpoints selected by EFSA (2015, 2023), the BfR (2023) and the FDA (2024).

Authority	Study	Key Endpoint	Approach taken	Health based guidance value
EFSA (2015)	CD-1 mouse, two generation study 0.003, 0.03, 0.3, 5, 50, 600 mg/kg bw/day in feed Tyl et al. (2008)	Changes in mean relative kidney weight $BMDL_{10}$: 8,960 µg/kg bw/day	Deterministic approach Human equivalent dose factor of 0.068 for oral exposure of mice (Doerge et al., 2011) was applied to the BMDL to derive a human equivalent dose of 609 µg/kg bw/day (RP) Total uncertainty factor of 150 Based on 2.5 for interspecies differences (2.5 for toxicodynamics, 1 for toxicokinetics), 10 for intraspecies differences and 6 for uncertainties in the data base	t-TDI: 4 µg/kg bw/day

EFSA (2023)	ICR mouse, gestational study; exposure: GD0 – PND21 0.475, 4.75, 47.5 µg/kg bw/day) in drinking water Luo et al. (2016)	Increase in percentage of Th17 cells $BMDL_{40}$: 0.53 µg/kg bw/day	Deterministic approach Toxicokinetic data in mice (Doerge et al., 2011) and adult humans (Teeguarden et al., 2015; Thayer et al., 2015) considered suitable for derivation of an oral HEDF Human equivalent dose factor of 0.0155 applied to derive human equivalent dose of 0.0082 µg/kg bw/day (POD) Total uncertainty factor of 50 Based on 2.5 for interspecies toxicodynamic differences, 10 for intraspecies toxicokinetics and toxicodynamics and 2 for uncertainty analysis	TDI: 0.0002 µg/kg bw/day
BfR (2023)	Male Wistar rat 2, 20, 200 µg/kg bw/day by gavage;	Reduced sperm count At 200 µg/kg $BMDL_{10}$: 26 µg/kg bw/day	Probabilistic approach No single human equivalent dose factor but a range (P05-P95) 0.2-1.55 based on toxicokinetic data in mice (Sieli et al., 2011; Taylor et al., 2011) and adult humans (Teeguarden et al., 2015; Thayer et al., 2015).	TDI: 0.2 µg/kg bw/day

	Exposure: 60 days Liu et al. (2013) 50, 500, 1000 µg/kg bw/day by gavage; Exposure: 90 days/3months Srivastava and Gupta (2018)	Liu et al. (2013) At 500 µg/kg bw/day NOAEL: 50 µg/kg bw/day Srivastava and Gupta (2018)	Range of TDIs calculated were 0.14-39 µg/kg bw/day and 0.2-78 µg/kg bw/day based on the studies by Liu et al. (2013) and Srivastava and Gupta (2018), respectively. Mean of the lower limit of the confidence intervals selected as TDI	
FDA (2024)	Rodent multigeneration studies CD-1 Swiss Mouse	Systemic toxicity NOAEL: 5000 µg/kg bw/day	Margin of safety approach Conclusions on safety of BPA based on consumer exposure and the NOAEL of 5000 µg/kg bw per day for systemic toxicity in rodents.	Maintained from 2008/2014

	0.003, 0.03, 0.3, 5, 50, 600 mg/kg bw/day via feed Sprague-Dawley rat 0.001, 0.02, 0.3, 5, 50, 500 mg/kg bw/day via feed	Reproductive effects NOAEL: 50,000 µg/kg bw/day Offspring NOAEL: 50,000 µg/kg bw/day		