

Report on divergent views between EFSA and EMA on EFSA's updated bisphenol A assessment

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1. Background

The European Food Safety Authority (EFSA) has carried out a re-evaluation of risks to public health related to the presence of bisphenol A (BPA) in foodstuffs. EFSA established a 20,000-fold lowering of the tolerable daily intake (TDI) for BPA from 4 µg/kg bw per day to 0.2 ng/kg bw per day.¹

A draft of this opinion underwent a public consultation from 15 December 2021 to 22 February 2022.² In this context the European Medicines Agency (EMA) provided several comments highlighting diverging views related to various aspects of the EFSA scientific assessment. EMA's comments were mainly linked to differences in scientific approaches to risk assessment and the methodology for quantifying the risk between EFSA and EMA. EFSA answered in detail to all the comments in Annex N of the opinion.¹

EMA is responsible for evaluating benefits and risks of medicines and medicine-device combinations. BPA may be present in primary packaging material and manufacturing equipment used in the manufacturing process of medicines, in medicine containers, medicine/device combinations, and in parenteral nutrition bags.ⁱ

The founding Regulations of EFSA and EMA, as well as a memorandum of understanding in place between the two Agencies, stipulate that they will cooperate to resolve any divergence of scientific view that may arise. For EFSA, this is laid down in Article 30 of Regulation (EC) No 178/2002 and for EMA, in Article 59 of Regulation (EC) No 726/2004. Where there is a substantive divergence over scientific issues that cannot be resolved, according to the respective founding regulations, EFSA and EMA are obliged to cooperate with a view to either resolving the divergence or presenting a joint document to the European Commission clarifying the contentious scientific issues and identifying the relevant uncertainties in the data. This document shall be made public.

In this context, a meeting was held between the two Agencies on 29 November 2022 to discuss the diverging views on the EFSA scientific opinion and to identify opportunities for possible convergence. Applicable methodologies for medicines are not only of relevance for Europe; they are discussed and used globally (e.g. as expressed in ICH guidelines of the International Council of Harmonization of Technical Requirements for Registration of Pharmaceuticals of Human Useⁱⁱ). The EMA position on a number of matters outlined in this document is informed by such globally agreed methodologies for approvals of medicines and discussions ongoing in ICH.

This document focuses on the key points of scientific divergence and has been written jointly between the Agencies for the attention of the European Commission (EC).

2. Points of scientific divergence

Discussion focused on the following points of scientific divergence:

ⁱ EMA's guideline on Plastic Immediate Packaging Materials can be found here: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-plastic-immediate-packaging-materials_en.pdf

ⁱⁱ ICH: the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; information available at <https://www.ich.org/>



- a) Adverse effect definition in the BPA assessment
- b) Intermediate endpoint (splenic Th17 percentage increase, ovarian follicle counts) versus apical endpoint (asthma, fertility)
- c) Approaches to studies included for consideration
- d) The two Agencies' risk assessment approaches (including clinical relevance of endpoints from animal studies for use in humans)

2a) Adverse effect definition in the BPA assessment

In its draft opinion, EFSA selected the increase of Th17 cell percentage in spleens of mice exposed during pregnancy³ as reference point to establish the health-based guidance value (HBGV) for the presence of BPA in foodstuffs and food contact materials. The second most sensitive endpoint identified was reduced ovarian follicle counts in mice⁴. Both reference points are intermediate endpoints and in accordance with EFSA guidelines for assessment both effects were considered as adverse. The definition of adversity used by EFSA⁵ makes no mention nor requirement for apicality of an effect to be considered adverse. In setting a HBGV, EFSA takes into account the effects which have a relationship with possible apical adverse effects and therefore potentially have toxicological relevance. However, such effects do not necessarily need to relate to an apical endpoint in a one-to-one causal association. EFSA includes the use of intermediate endpoints considered having a clear causal correlation with an adverse outcome (AO). EFSA deems that by weighting the overall body of evidence according to the established protocol, it is possible to identify a link between an intermediate effect and an AO, even though the AO is *not necessarily expressed within the design and scope of the studies considered* and is not necessarily confirmed in a single study. The evidence reviewed in the opinion (Section 3.1.3), as well as the increasing scientific evidence on BPA effects (see response to comment 30 in Annex N), was considered to clearly show that an increment in the Th17 cell percentage and their interleukins (IL) are involved, both in experimental animals and in humans, in various immune-mediated disorders related to inflammatory pathogenesis (e.g. psoriasis, diabetes, multiple sclerosis, neutrophilic asthma, etc.). Moreover, there are also human studies that link Th17 cells related effects to inflammation. In particular, there is clinical success of targeting the IL-17/IL-23 axis in chronic inflammation of body lining, while for internal organs this is less clear⁶. Therefore, based on the current definitions from WHO/IPCS used by EFSA, intermediate endpoints, such as Th17 cell percentage increase, according to EFSA can be considered adverse effects and, depending on the available information, used as reference point to establish a HBGV.

EMA considers the pathogenesis, mode of action leading to the adverse effect(s) and clinical or histopathological evidence of organ damage based on biological significance and biological plausibility, *within the design and scope of studies performed*. Following on from that, evidence generation and confirmation of clinical relevance may happen (e.g. in follow-up studies) when there is a signal of potential harm. EMA does not dispute increased Th17 cell counts and reduced ovarian follicle counts were observed in mice. However, EMA takes a different scientific approach when considering the implications of these observations for human exposure, requiring evidence of causality. According to EMA, there is insufficient evidence to support EFSA's claims that Th17 cell increases in mice lead to an increased risk of IgE-mediated immune disorders in humans; additionally, EMA considers that the isolated observation of reduced ovarian follicle counts in a single mice study cannot be interpreted to signify impairment of fertility in humans.



Therefore, there is no agreement between the Agencies regarding what constitutes 'a clear causal relationship' between intermediate and apical endpoints, and hence an adverse effect, as outlined below.

2b) Intermediate endpoint versus apical endpoint

As to the increased percentage in Th17 cells, according to EMA, there is no evidence from the studies included by EFSA that the observed increase in Th17 cells (which is not disputed) resulted in any AO. Moreover, studies within the NTP CLARITY-BPA program, which is a program that encompasses a wide range of robustly carried out toxicity studies, including studies of BPA toxicity, under the National Toxicology Program of the United States Department of Health and Human Services, provided no evidence for immunotoxicity at low doses.⁷ In summary, according to EMA, current scientific understanding does not support a causal link between Th17 cells and IgE-mediated allergy.

EFSA agrees that there is no direct causal link between Th17 and IgE mediated allergy, as clearly stated in the current opinion and explained in the Annex N of the opinion. However, EFSA highlighted that, even in the absence of a quantitative Adverse Outcome Pathway (AOP), evidence for a link between Th17 cells and several AOs exists, since Th17 cells and their ILs are involved in diseases with an inflammatory pathogenesis, such as for instance psoriasis and asthma^{8 9}, as reported in Section 3.1.3 of the opinion. Additionally, the probability of this association was quantified by the expert knowledge elicitation performed in the context of the uncertainty analysis exercise (see Section 3.2.3 and Appendix D in the opinion). Finally, EFSA reiterated that the NTP CLARITY-BPA program did not investigate Th17 cells in mice.

In response, EMA referred to the fact the Grantee study addressing immunotoxicity in rats showed very limited effects, which were not dose-related and did not show consistent trends throughout time¹⁰. However, EFSA highlighted that neither this study investigated Th17 cells.

EFSA BPA Working Group members and EMA NcWP members discussed their analyses and relevant Agencies' guidance documents^{11 12 13}, including the matter of biological plausibility and scientific rationale for a causal link (outlined below). Divergence of opinion between the Agencies on intermediate versus apical endpoints remains.

Summarising the differences of opinion on Th17 cells,

- The conclusions of EFSA's opinion are based on the weight of evidence assessment of a large number of studies and clusters of endpoints for Immunotoxicity and also other seven Health Outcome Categories (see Section 3.1 of the opinion and Annex H). The effect of Th17 cell percentage in mice were also confirmed in more recent studies, showing effects at the same dose range (Section 3.1.3 and response to comment 30 in Annex N). This is not disputed by EMA. However, the relevance in humans such as the evidence related to allergy, the species difference, as well as human variability concerning immune response, as addressed in the EFSA opinion, is questioned. EMA considers indeed there is insufficient evidence to conclude on the biological plausibility of a causal association between Th17 cell percentage and immune disorders, especially given that a causal link has not been demonstrated in a study in animals or humans.
- EFSA has applied the Human-Equivalent-Dose-Factor (HEDF) concept to convert BPA doses from animals to humans, as per its current guidance document¹³. EFSA acknowledges that it may be appropriate to apply specific factors when extrapolating from intermediate endpoints in animals to apical endpoints in humans. However, in this assessment extrapolation factors of this type were not quantified due to lack of relevant quantitative



data and specific Guidance. In EMA's view, some effects in animals are not seen in humans and this has implications for the translation of findings on intermediate endpoints from animal studies to health effects in humans. In the absence of quantitative data to support an animal-to-human extrapolation, any statement on the relevance for humans are challenging if it is not substantiated by data.

As to the second most sensitive endpoint, the reduction in ovarian follicle counts, this was discussed together with another reproductive endpoint used, i.e. sperm motility. For this endpoint both Agencies agree the studies considered pivotal by EFSA were not fertility studies compliant with the OECDⁱⁱⁱ and ICH guidelines^{12 14 15}: they mainly investigate mechanistic rather than toxicological endpoints.

- According to EFSA, in the current evaluation, new evidence has emerged on reproductive and developmental toxicity, including evidence on new endpoints and on endpoints not previously assessed at all doses¹⁶, which strengthens the evidence for adverse effects on reproductive and developmental toxicity. In particular, it was noted that the sperm parameters observed and reported in the BPA opinion¹⁷ are endpoints that have already been used in previous EFSA risk assessments (e.g., dioxins). In the case of altered oocyte/follicle counts reported in Hu et al. (2018)⁴, the CEP panel considered it relevant and consistent with premature reproductive senescence observed in females. This is an endpoint that would not be tested in guideline studies.
- According to EMA, there is no scientific evidence that reduced follicle count or reduced sperm motility as single endpoints observed in the studies used by EFSA would result in reduced fertility in humans. Both studies^{4 17} can be considered to be mainly mechanistic studies not investigating the toxicological endpoints causative for adverse effects on fertility as would be done in a fertility study according to OECD 443. Furthermore, there is evidence that rodents are able to compensate for reduced sperm motility and that from this endpoint alone no conclusion can be drawn with regard to impaired fertility in male rodents.¹⁸¹⁸ In addition, there is no clear cut correlation to reduced male human fertility if used as stand-alone endpoint. The study by Hu et al. has some additional limitations e.g. no individual follicle counts were presented but instead, only ratios. Also, from the effects presented by Hu et al, according to EMA it is not possible to conclude on impaired fertility in female mice induced by BPA. Based on both studies therefore, according to EMA no conclusion can be drawn from the effects after BPA treatment in rodents to adverse effects on fertility in humans. According to EMA, these studies cannot be used to conclude on fertility impairment in mice induced by BPA starting at a dose of 10 µg/kg/d and therefore cannot be taken for benchmark dose analysis.
- It became clear from the discussion that both EFSA and EMA may accept intermediate endpoints in hazard and/or risk assessment. However, for EMA to accept such intermediate endpoints as sufficient to be used as reference point, direct evidence is required to demonstrate the intermediate endpoint is in the causal pathway to, and closely causally associated with, the adverse effect of concern. This evidence needs to be within the design and scope of the studies.
- EFSA also agrees that for an adverse intermediate endpoint to be used in risk assessment, it needs to have a causal link with an apical AO. However, if the weight of the overall evidence evaluated by EFSA's rigorous scientific method and supported by data from mode of action studies, provides sufficient indications of the existence of a causal link between the two, EFSA considers an intermediate endpoint adequate to be used for establishing a

ⁱⁱⁱ OECD: the The Organisation for Economic Co-operation and Development; information available at <https://www.oecd.org/>



HBGV even in the absence of a direct causal pathway reported within the design and scope of the studies. EFSA then applies uncertainty factors to quantify the likelihood of leading from an adverse intermediate endpoint to an apical adverse outcome.

2c) Approaches to studies included for consideration

EMA and EFSA apply different methods for quantifying risk in humans.

When applicants seek *marketing authorisation* for their medicines, they submit data from guideline studies carried out under GLP conditions as pivotal studies. EMA uses toxicokinetics data from the GLP studies to calculate safety margins based on the no observed adverse effect level (NOAEL) as well as prediction of human exposure with preliminary pharmacokinetic data to understand at which dose the substance would be considered harmful to humans. EMA, for *active substances as well as novel excipients in marketing authorisation procedures*, requires studies are carried out in accordance with GLP and GCP guidelines. However, robust non-GLP studies can be taken into consideration to support the evaluation and may contribute to the full assessment. *For impurities*, EMA accepts reference to the scientific literature and allows marketing authorisation holders / applicants to calculate permissible daily exposures based on that data. Given that BPA may migrate in trace amounts into liquid-containing packaging due to contact with essential packaging materials, if it does appear in medicines, this is considered a leachable impurity. Additionally, for safety signals in the post-authorisation phase, other (non-clinical, clinical and observational) studies from the scientific literature are also included for consideration provided they are sufficiently robust.

EFSA was mandated to carry out a re-evaluation of the risks to public health related to the presence of BPA in foodstuffs. This is not a safety assessment for a specific application of a substance, and for this reason EFSA was not provided with specific guidelines studies. EFSA used a systematic approach according to a pre-established protocol, which included critical appraisal and assessment of the weight of evidence¹¹ of all the available guidelines studies and of the academic non-guidelines studies, as is the case for many other EU risk assessments.

2d) Comparison of the two Agencies' risk assessment approaches

As a general principle, to approve medicines, EMA performs a risk assessment based on quantification of risk. This allows EMA to establish doses at which the exposure to a specific substance such as excipients and leachable impurities would have no adverse effect when administered to patients.

For acceptance of studies to quantify risk EMA needs reliable evidence i.e.:

- Apical endpoints to minimise and avoid uncertainty;
- A clear causality between exposure and the adverse effect, based on the pathogenesis of the effect(s) and clinical or histopathological evidence of organ damage, with the evaluation taking into account biological significance and plausibility;
- Human relevance of the observed effects;
- Data integrity especially for quantification purposes (i.e., calculation of safety margins).

Within EFSA's risk assessment framework, the TDI is established as a protective dose at which no health effects occur to the general population based on a lifelong dietary exposure. Exceeding a TDI might not invariably lead to an adverse health effect in humans, as it depends on a number of factors such as for example dose, magnitude of the effect, time and/or duration



of the exposure exceedance. Contributing to the low TDI established in the BPA opinion is the use of uncertainty factors to extrapolate from animal studies to human, according to the EFSA guidance documents^{13 19}. In the BPA opinion, EFSA has applied the HEDF, which is a substance-specific factor, for the interspecies toxicokinetic differences, and the default values for the interspecies toxicodynamic and the intraspecies toxicokinetic and dynamic uncertainty factors, as provided in its current guidance documents¹³. Furthermore, the various uncertainties affecting the BPA assessment were taken into consideration by determining an additional uncertainty factor giving rise to a lowered TDI, which was then considered the final TDI, in accordance with current EFSA guidance documents.^{13 19}

3. Conclusions

- Taking into account the EFSA draft opinion, comments received in the public consultation, EFSA's responses, the information exchange and discussion on 29 November 2022, and for reasons outlined in this document, EMA is not in agreement with the currently revised TDI.
- It is not possible to achieve convergence for the differences of opinion regarding the appropriate TDI for BPA between the two Agencies, because in line with their respective guidelines, the Agencies make use of different assessment tools, different methodologies to interpret and quantify risk for humans, they have a different purpose, and they rely on different definitions of adversity. The weight of evidence given to studies for consideration, as well as the interpretation of the data included, will therefore be different between the two Agencies.

The two major points of divergence between the two Agencies can be summarised as follows:

- 1) EFSA and EMA do not agree on what can be considered sufficient scientific evidence to demonstrate the claim that the intermediate endpoints identified in animals in the newly included studies are causally associated with the adverse effects of concern in humans
- 2) EFSA and EMA do not agree on the method to quantify the risk and establish at which exposure levels BPA can be considered safe in humans.

Both EMA and EFSA also acknowledge the importance of further constructive dialogue between EU Agencies, Member State national authorities as well as risk communication and management of experts for future alignment of the methodologies applied, as foreseen by the One Substance One Assessment approach under the EC Chemical Strategy for Sustainability.



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