HBM4EU: Contribution to the Public Consultation on the draft scientific opinion of the EFSA CEP Panel on the Re-evaluation of the risks to the public health related to the presence of bisphenol A (BPA) in foodstuffs.

HBM4EU, **the human biomonitoring initiative in Europe** from 2017 to June 2022, is investigating the exposure and the health effects resulting from exposure to 18 priority chemical substance groups including bisphenols and BPA.

One of the main goals of HBM4EU is to strengthen the science-policy interface in the European Union and to support informed decision making. Therefore, HBM4EU would like to make a statement in the Public Consultation of the Scientific Opinion of the EFSA CEP Panel on the Re-evaluation of the risks to the public health related to the presence of BPA in foodstuffs.

HBM4EU strongly welcomes the scientific opinion, acknowledges its scientific excellence, and highly values the new evaluation of BPA and the establishment of a full TDI in the current proposal.

Bisphenol A is addressed in all pillars and several work packages of HBM4EU: from the science to policy interface in Pillar 1 and use of human biomonitoring to improve risk assessment, as well as in Pillar 2, covering aligned studies, harmonized methods and data management and in Pillar 3, where research on health effects, including modelling, adverse outcome pathways, effect biomarkers, evaluation of cohort studies and mixture effects are performed.

HBM4EU results are published in peer reviewed journals as well as on the HBM4EU website in the section deliverables[1].

The EFSA CEP Panel has performed the re-evaluation of EFSA t-TDI for BPA established in 2015. The CEP Panel concludes that it is Unlikely to Very Unlikely that BPA presents a genotoxic hazard through a direct mechanism. Therefore, it is concluded that the balance of evidence allows a health-based guidance value (HBGV) to be established.

The immune system has been identified as the most sensitive health outcome category to BPA exposure in the scientific opinion of EFSA. Specifically, an **increase of Th17 cells** was identified as the critical effect; these cells are pivotal in cellular immune mechanisms and involved in the development of allergic lung inflammation. The immunotoxic effects of BPA, observed both in experimental animals as well as in human epidemiological studies (Casas & Gascon, 2020; Li et al. 2018a, b), are selected as most sensitive end-point of concern. Other endpoints have also been considered including endocrine and metabolic outcomes for which a wealth of studies are available in the literature. We have several comments on the draft:

- ***Relevance of additional health endpoints***. Several endocrine and metabolic endpoints (in addition to other endpoints) have been shown to be relevant in the EFSA opinion and BMDLs are available for some of them (e.g., ovarian follicle count, uric acid). They appear to display similar sensitivity to the immune response (within 1 to 2 orders of magnitude). It is important to note that the links between BPA and endocrine, neuroendocrine and metabolic endpoints are supported by dozens of academic reviews including meta-analysis of both animal and human evidence (Wassenaar et al. 2017; Peluso et al. 2014, Rochester et al. 2018; Ribeiro et al. 2020; Wu et al. 2020; Pergialiotis et al. 2018; Hwang et al. 2018; Nowak et al. 2019). HBM4EU recommends to calculate TDIs based on all relevant sensitive outcomes and compare intakes to those TDIs. We presume that this is likely to show that human exposure is significantly above these different TDIs. Such tests would actually strengthen the EFSA conclusions for drastically decreasing the TDI based on the immune effects.
- **Using AOPs to rationalize effect marker selection**. The increase in the number of Th17 is used to derive the new TDI, and this is indeed supported by a number of studies. In HBM4EU we have developed an approach for the selection of relevant effect markers based on the AOP

[1] HBM4EU deliverables

framework[2]. Moreover, HBM4EU partners have identified and prioritized existing biomarkers of effect for BPA, as well as provided relevant mechanistic and adverse outcome pathway (AOP) in order to cover knowledge gaps and better interpret effect biomarker data (Mustieles et al. 2020). We believe this would constitute a generic approach linking AOPs to effect marker and adverse outcome selection. There are indeed few AOPs that have been developed in immunotoxicity[3] (Sabuz-Vidal et al. 2022), so this is a call for action to further develop such AOPs and to use them for effect marker and adverse outcome selection in both toxicological and human studies.

- ***Comprehensive use of human data.*** HBM4EU generates human biomonitoring data in dedicated surveys and analyzes cohort data. Human data were documented and used in the opinion. Most led to conclusions such "Unlikely" or "As Likely As Not (ALAN)". There is a wealth of cohort studies linking BPA to endocrine and metabolic effects and it is unclear to us whether they were all considered and why the conclusions were rather negative or neutral. Globally the draft relies heavily on animal studies, when we think that inclusion of more human data would be beneficial (Vom Saal et al. 2021; Ejaredar et al. 2027; Rancière et al. 2015). One approach would be, once a full TDI is released, to validate it using the human data that are available. This can be carried out by comparing human biomonitoring guidance values (HBM-GVs) derived on the new TDI basis with further human data based on a relationship between internal concentrations and health effects according to options 2 and 1 respectively of the HBM4EU strategy to derive HBM guidance values (Apel et al. 2020). The provisional HBM-GVs recalculated based on the full TDI using PBPK modelling are 2.3 ng total BPA/l urine for adults and 1.4 ng total BPA/l urine for children assuming 100% oral intake in each case (communicated by Florence Zeman and Céline Brochot).
- ***Analytical methods.*** An additional issue is that such low levels of guidance values may be below the detection limits of analytical methods. This raises a new challenge to further improve the sensitivity of detection.
- ***Mixture effects and substituents***. The current opinion does not address the mixture question regarding BPA substitutes/alternatives like BPS and BPF. This scope is important since BPA alternatives are now used and much of their effects are similar to those of BPA. Thus, a mixture approach seems appropriate and would be in line with the current concern about mixture effects. Furthermore, it is likely that the current EFSA TDI will lead to an increased use of BPA substituents - e.g., BPF, BPS, and BPAF are among the main substitutes of BPA (Chen et al., 2016) particularly if the current TDI's for these substituents are relatively high. If these substituents display similar effects to BPA, as suggested by previous review works (Rochester & Bolden, 2015; Carvaillo et al. 2019; Rugard et al. 2020) it is urgent to revise their TDIs to avoid regrettable substitutions. New epidemiological research including HBM for exposure biomarkers (for BPA substitutes) as well as effect biomarkers (like Th17) seems to be crucial here.
- ***Impacts on citizens' faith in science*.** The recent EFSA opinion defines a tolerable daily intake of 0.04 ng BPA/kg bw per day for BPA. Comparison of this TDI with the dietary exposure estimates from the EFSA 2015 opinion showed that both the mean and the 95th percentile **dietary exposures in all age groups exceed the TDI by two to four orders of magnitude**. The EFSA CEP Panel concludes that there is a health concern from dietary BPA exposure for all age groups. It would be important to consider in the draft opinion possible citizens and stakeholders concerns on their exposure over time to BPA doses highly exceeding the new TDI value as well as on the related health impact in the future. Also, since the new TDI is 5 orders of magnitude below the previous one, citizens may not understand such a huge change in this HBGV. This may fuel additional doubts on risk assessment methods/decisions and should be explained with

[2] Additional Deliverable 14.3 - WP14 - WP13 Interaction: Delineation of AOPs for the selection of effect biomarkers in the HBM4EU aligned studies Bisphenol A as a case-study

[3] Collaborative Adverse Outcome Pathway Wiki (AOP-Wiki)

transparency. Communication to the citizens on how potential risks are evaluated and managed is critical at this stage.

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