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Critical Evaluation of Immunotoxicity Data Used as the Basis for a Tolerable Daily Intake for Bisphenol A

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In 2023, the European Food Safety Authority (EFSA) published a hazard assessment of bisphenol A (BPA), based on a limited subset of relevant studies, and derived a tolerable daily intake (TDI) for BPA that is several orders of magnitude lower than EFSA's temporary TDI established in 2015. The current TDI is based on the immunological endpoint of increased percentage of Th17 cells in the spleen of mice exposed to very low doses of BPA. In order to associate this intermediate endpoint to an adverse outcome, EFSA hypothesized that an increased Th17 cell percentage is a key event in the development of allergic lung inflammation. The hazard assessment excluded multiple high-quality studies, did not constitute a true weight-of-evidence evaluation, and resulted in very sensitive endpoints with unclear connections to apical toxicity being chosen to characterize BPA toxicity. We investigated whether an increased percentage of Th17 cells represents an adverse, human-relevant effect of BPA with a functional immune consequence that is consistent and coherent across studies, and if this immunological endpoint is scientifically justified as a basis for deriving a TDI. We critically analyzed all available rodent studies of BPA examining Th17 cell percentage, as well as potentially related endpoints (IL-17 levels, IgE levels, and allergic lung inflammation). We assessed the results of the studies in the context of study quality and integrated their results using multiple criteria, including consistency, coherence, and the adversity and human relevance of the effects. We tabulated the study results in a systematic manner, such that positive, negative, or null changes in each individual endpoint were recorded separately for each dose level examined. This allowed for the consistency of results across doses, time points, sexes, and tissue types to be easily discerned. Our evaluation of study quality considered factors such as number of animals, exposure assessment, and blinding of investigators to dose groups. To evaluate coherence, we assessed whether interpretation of the results is consistent with what is known about BPA and immunotoxicity across rodent and human studies. Our analysis showed that BPA-induced changes in Th17 cell percentage differed across sexes, time points, tissue types, and doses, and an increase in this endpoint was not consistently observed across studies. The reported increases were transient and of small magnitude, indicating a lack of adversity. The studies were only conducted in mice, used small numbers of animals, did not blind investigators to dose groups, and used *ex vivo* methods that are not physiologically relevant to measure the outcome. The Th17 cell endpoint is not relevant to humans, and epidemiology studies of BPA exposure and the potential downstream effects of allergy or asthma are inconsistent and inconclusive. Studies of related endpoints (IL-17 levels, IgE levels, and airway inflammation) using similar BPA doses reported inconsistent but largely null results across studies, indicating that BPA has no clear effect on the potential downstream, adverse endpoint of allergic lung inflammation in rodents. This analysis indicates that an increase in Th17 cell percentage in the mouse spleen is not a reliable endpoint for deriving a TDI, and it is not consistent with high-quality guideline studies showing a lack of immunotoxic effects at low BPA doses in rats and mice. Overall, our critical analysis indicates that the increased Th17 cell percentage used as the basis of EFSA's TDI for BPA is an intermediate endpoint that is not adverse nor a precursor event to any downstream pathological outcome, such as allergic lung inflammation; is not consistent or coherent across studies; and, therefore, is not scientifically justified as the basis for the TDI. The EFSA-derived TDI is several orders of magnitude lower than estimates of safe doses of BPA established by agencies worldwide, and BPA has been used safely over the years for all intended uses based on these

established safe dose estimates. The TDI is also several orders of magnitude lower than dietary exposure estimates of BPA, at which there is no clear evidence for adverse effects on the immune system in general observations of human populations. Future assessments that seek to develop safe dose estimates of BPA (or any substance) should include all available evidence; consider the reliability of study results; and choose endpoints that are either adverse, apical effects or their precursors that are both consistent and coherent across studies in experimental animals and humans.