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Critical Analysis of Sperm Parameter Data Used as the Basis for a Tolerable Daily Intake for Bisphenol A

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The German Federal Institute for Risk Assessment (BfR) recently criticized the tolerable daily intake (TDI) established for bisphenol A (BPA) in 2023 by the European Food Safety Authority (EFSA) and established its own TDI for BPA. Similar to EFSA's TDI, the BfR TDI was based on a review of a limited subset of relevant studies, which did not include multiple high-quality studies and did not constitute a true weight-of-evidence evaluation. The specific endpoint that forms the basis of the BfR TDI is reduced sperm count in rats exposed to BPA during adulthood, as reported in two studies that the BfR did not consider to be of high quality and for which the results were contradictory with studies using other exposure scenarios. We examined whether reduced sperm count in rats represents an adverse, human-relevant effect of BPA with a functional deficit in male fertility that is consistent and coherent across studies and is scientifically justified as a basis for deriving a TDI. We critically analyzed all available rodent studies of BPA examining sperm count, as well as related endpoints (testis weight, sperm viability, sperm motility, and sperm morphology). 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, generations, and exposure scenarios 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 male reproductive effects across rodent and human studies. Our analysis showed that BPA-induced changes in sperm count differed across species, doses, time points, generations, and exposure scenarios, and a decrease in this endpoint was not consistently observed across studies. High-quality guideline studies do not report effects on sperm count with either perinatal or adult exposure to low doses of BPA. Studies of related endpoints (testis weight, sperm viability, sperm motility, and sperm morphology) reported largely null results across studies, particularly in high-quality guideline studies, indicating that BPA does not have clear and consistent effects on sperm parameters. The few testicular or sperm effects reported in the high-quality guideline studies were observed only at very high doses that were associated with systemic toxicity. In addition, there is a lack of evidence for BPA exposure causing male infertility in high-quality studies, such as two- and three-generation reproductive toxicity studies in rodents, indicating that the sperm parameter alterations reported in certain studies do not lead to functional deficits in male fertility. Epidemiology studies also indicate that there are no clear or consistent associations between BPA exposure and endpoints related to male infertility. This analysis indicates that a decreased sperm count in rats exposed to BPA during adulthood is not a reliable endpoint for deriving a TDI, and it is not consistent with high-quality guideline studies showing a lack of consistent effects on sperm parameters at low BPA doses in rodents, as well as with human and rodent studies showing no associations between BPA exposure and adverse effects on male fertility. Overall, our critical analysis indicates that the endpoint of decreased sperm count in rats used as the basis of BfR's TDI for BPA is not consistent or coherent across studies; is not clearly relevant to humans nor associated with adverse effects on male fertility; and, therefore, is not scientifically justified as the basis for a regulatory value. The resulting TDI is 1-2 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. 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 adverse, human-relevant effects that are both consistent and coherent across studies in experimental animals and humans.