TEDX
The Endocrine Disruption Exchange

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Comments on **SYSTEMATIC REVIEW OF IMMUNOTOXICITY ASSOCIATED WITH EXPOSURE TO PERFLUOROOCTANOIC ACID (PFOA) OR PERFLUOROOCTANE SULFONATE (PFOS)**

TEDX (The Endocrine Disruption Exchange) is a non-governmental organization that compiles, analyzes, and disseminates scientific information on chemicals that affect health and the environment. We have used the systematic review method developed by the National Toxicology Program's Office of Health Assessment and Translation (OHAT) in various capacities for our work. We are providing comments on this method as presented in the "Systematic Review of Immunotoxicity associated with exposure to Perfluorooctanoic Acid (PFOA) or Perfluorooctane Sulfonate (PFOS)."

This review is an impressive example of the capacity of the National Toxicology Program (NTP) to produce a thorough, detailed, and accurate assessment of the available science using the relatively new systematic review methods developed by OHAT. The HAWC generated tables and figures provide a rich data resource for researchers, regulatory decision makers, and the general public. We hope this detailed information will continue to be available long-term and that its existence will be made widely known among scientists studying the immunotoxicity of PFOA and PFOS.

However, given the amount of data and the multiple ways to access it, we suggest that NTP make an effort to identify and train end-users in how to navigate the interactive tables and figures. Our concern is that the comprehensiveness and detail of the data provided may lengthen the time needed to conduct and interpret such systematic reviews for practical purposes. We further suggest that NTP directly solicit feedback from intended audiences on the usefulness of the review including the interactive data tables and figures. While these detailed reports may be useful for scientists, the degree to which they will be studied and used, for regulatory decision making should be clearly understood so that identification of hazardous chemicals is not delayed.

We had one specific comment: on Page 21, it is stated that "confidence conclusions were considered with and without high risk of bias studies (e.g., studies rating probably high or definitively high risk of bias for two key risk-of-bias questions) to assess the impact of the high risk of bias studies." However, we did not see further discussion of this approach in the document. Please indicate the results of this sensitivity analysis.

We were pleased to see such a thorough explanation of how mechanistic and other supporting evidence can be used in conducting systematic reviews. Unfortunately, the mechanistic data were not informative to this review. Perhaps it would have been more efficient to determine this before the review was conducted, (e.g., during protocol development). Also, please clarify in the current report how dose response and potency will be used in future reviews to contribute to

conclusions regarding biological plausibility. For example, it is unclear why cellular events must occur at the same or lower doses than in vivo health effects to be included as support.

In our opinion, one of the most important uses of systematic reviews is to guide the most efficient use of future funding to address outstanding research questions identified in the review. We felt the review would benefit from renaming the "Limitations of the Evidence Base" section in order to highlight its purpose of identifying future research needs (e.g., prospective epidemiological studies; studies of ulcerative colitis). This, however, raises questions of how much more research is truly needed. This particular review concluded there was high confidence in the animal literature on both chemicals. This would suggest that further research in animals on the immunotoxicity of PFOA and PFOS may not be necessary. Such conclusions should be explicitly stated in the review, and perhaps more importantly, made known to relevant research funding agencies.

The other important use of systematic review is in guiding regulatory decisions to prevent harm to public health. It is unclear how the hazard ID ratings translate to such decisions. Is a "presumed" hazard ID rating for PFOA and PFOS enough to trigger regulatory controls? If determinations about the continued use or release of a chemical can be made using this level of evidence, perhaps no further research is necessary. Such efficient use of systematic review to save time, money, and effort should be highly valued by the public and federal government. A discussion of the utility of the hazard ID ratings in the context of regulation should be included in the report.

Overall, we are pleased to see the NTP conducting environmental health systematic reviews, based on their extensive development of methods. This specific review provides a wealth of information on the impact of PFOA and PFOS on immune endpoints. We thank you for accepting our public comments on this review and the OHAT process.

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