

Dear Colleagues

We appreciate the opportunity to provide comments on this review of EPA's draft text entitled "EXTERNAL PEER REVIEW DRAFT, Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal for Perfluorooctanoic Acid (PFOA) (CASRN 335-67-1) in Drinking Water. This text is well written in many places and summarizes most of the literature in a balanced and scientifically appropriate way. We wish to bring to your attention information in three areas that might improve the text.

First, EPA's discussion of critical effect does not fully explain the dose-imbalance in endpoints between human observational studies and experimental animal studies. For example,

- The human observational studies of immune effects and developmental toxicity generally occurred at much lower levels than in the definitive experimental animal studies.
 - This can be due to the differences in kinetics between human and experimental animals, or in sensitivities between humans and experimental animals, or to the fact that many of the human studies are observational, not causal.
 - Therefore, we encourage EPA SAB to carefully review this disparity in dose between epidemiology and toxicological findings, and make recommendations as appropriate.
- Depending on the critical effect, the PFOA or other PFAS half-life analysis may need to be reworked. For example:
 - If the critical effect is judged to be developmental toxicity, or other toxicity related to *in utero* exposure, then the proper dosimeter between experimental animals and humans or among humans may be the C_{max}, which is the default position of EPA (1991). An unfunded and award-winning publication describes this situation (Dourson et al., 2019).
 - If the critical effect is judged to be toxicity after a lengthy exposure, such as after 90 days or two years in experimental animals or chronic exposure in humans, then the proper dosimeter between experimental animals and humans may be the clearance by kidney and other organs, or if volumes of distribution are known between experimental animals and humans or among humans, then comparisons of half-life.

Second, the discussion of PFOA half-life is missing significant information, in part due to recent international developments and in part due to misunderstandings. Specifically:

- An unfunded and international collaboration has recently yielded a consensus position on the human half-life of PFOA (ARA, 2021a) of 0.5 to 1.5 years. This consensus was



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developed under the auspices of the Alliance for Risk Assessment

(<https://tera.org/Alliance%20for%20Risk/index.htm>) and is attached.

- An older human observational study by Zhang et al. (2013) is actually a clearance study where PFOA and its branch-chain isomers were monitored. The use of this study would avoid problems associated with unmonitored PFOA exposures and unmeasured PFOA isomers since all exposures are integrated into the blood. The average half-life in this study is 1.3 years and would be lower if other sources of elimination would have been monitored (*ARA*, 2021a).
- Most human observational studies do not account for unmonitored PFOA exposures and unmeasured PFOA branched isomers. The former problem would lead to an inflated PFOA half-life, the latter problem would lead to a deflated PFOA half-life. The two problems together result in unreducible uncertainty to the estimated half-lives in most of these observational studies (*ARA*, 2021a).
- A recent and unfunded publication gives a range of the PFOA half-life of 0.5 to 1.5 years based on human observational studies, a human clinical study, and an analysis of likely unmonitored PFOA exposures (Dourson and Gadagbui, 2021). A recent analysis of Nilsson et al. (2010) lends support to the lower limit of this range (*ARA*, 2021b, Figure 4, page 40).

Third, although sundry, the following items need attention:

- The citation of Dourson and Gadagbui (2021) related to the volume of distribution was surprising. The research in this publication was devoted to the PFOA half-life, using in part the only clinical study to date on PFOA. The volume of distribution was described in an appendix of this paper and noted to as an initial volume of distribution. A further analysis of this volume has been summarized in *ARA* (2021b, Figure 3, page 39).
- The draft value of the PFOA RfD given by EPA was shocking, since it is lower than the LD50 for botulin toxin, which is generally acknowledged to be the most toxic chemical known. If true, then EPA will need to carefully justify their position because otherwise it will likely be ridiculed.

Sincerely,

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