Office of Management and Budget (OMB) and Office of Science and Technology Policy (OSTP)
Comments on the Interagency Science Consultation
Draft IRIS Toxicological Review of Perfluorodecanoic Acid (PFDA)
March 2022
(Date Received April 14, 2022)

Dear EPA IRIS:

Thank you for the opportunity to provide comments on the draft Toxicological Review of PFDA. Overall, we found the analyses thorough and well-written. We have comments on sections throughout the text.

Major Comments

1. Executive Summary: "The ability to draw conclusions regarding these associations is limited (with the exception of immune [i.e., decreased antibody responses] and developmental [i.e., decreased birth weight] effects) by the overall quality of the studies (studies were generally low confidence); the few studies per health outcome; and, in some studies, the lack of a quantifiable measure of exposure." However, EPA has the same conclusion around hazard identification for liver, immune, developmental, and female and male reproductive effects. EPA concludes for all of these that the "evidence indicates" a likely association between exposure to PFDA and these effects in humans.
    a. More context is needed on how EPA can confidently make both of these statements. Such a wide range of interpretation of effects in humans continues to pose challenges to reviewers to follow the reasoning of the final evidence integration.

2. Exposure - Human Biomonitoring – consider adding in information from the ATSDR Exposure Assessments that were recently released. Points of contact are listed on ATSDR's websites and we recommend EPA consider reaching out for more information or available data.
    a. For New Castle, DE, see the following
        i. https://www.atsdr.cdc.gov/pfas/activities/assessments/sites/new-castle-countyde.html#Results
        ii. https://www.atsdr.cdc.gov/pfas/docs/ATSDR-PFAS-EA-Site-C-NewCastleCounty-Report-508.pdf
    b. For Spokane, WA, see the following
        i. https://www.atsdr.cdc.gov/pfas/activities/assessments/sites/spokane-countywa.html#Results
        ii. https://www.atsdr.cdc.gov/pfas/docs/ATSDR-PFAS-EA-Site-D-SpokaneCountyReport-508.pdf

3. Environmental Fate and Transport: there is a lot of generic information on PFAS in this section that is not specific to PFDA. It would be better to have PFDA-specific information or acknowledge that that information is not available. We observe this trend of referring to PFAS in general across sections. It is especially prominent in the fate and transport section, but all sections should emphasize the information available for PFDA. We suggest that in each section EPA consider

breaking the information out between what is generally known about other PFAS (and may be informative to properties of PFDA) and what is specifically known about PFDA.

4. Read Across: EPA seems to inconsistently rely on read-across analyses of PFAS assessments. Sometimes, EPA is looking towards the evidence base for similar PFAS species (e.g., PFBA), and other times that is not considered (e.g., PFBS). Based on the reliance on general PFAS data for the PK section, it seems that some read-across evidence for health effects may also be warranted. Can EPA comment on their decision framework when they choose to use data from other PFAS data to support their conclusions?

5. Page 3-157- Reproductive Toxicity – It would be helpful for EPA to specifically indicate for which of the 5 cited criteria the evidence of PFDA toxicity are met for female reproductive parameters in rats.
   For example, this reader did not see discussion of pseudopregnancy in the data analysis section. Was there evidence of pseudopregnancy?

6. Immune endpoints: Epidemiology:
   a. This population is exposed to other immunotoxicants (e.g., PCBs) in addition to PFAS. Please comment on whether those exposures could have contributed to confounding in the observed effects.
   b. Antibody response – is there a biologically supported cut-point for change in antibody production that indicates immunotoxicity? The range of changes was 2-25% in the critical studies. Is a 2% difference indicative of immunotoxicity?
   c. Are these antibody titers (from the Grandjean et al., 2012, 2017a, and 2017b studies) logtransformed? How does that impact the understanding of a percentage change?
   d. Does a 5% change in antibody concentrations equate to risk for developing tetanus? i.e., does this change put someone in a "non-protective" level of antibody levels? Please provide support (i.e., clinical relevance) for this being a meaningful cut point in antibody concentration for risk, especially given the wide distribution of normal titers.
   e. BMD/BMDL: Appendix C suggests that PFOA and PFOS significantly attenuate the association between PFDA and antibody levels. It seems like EPA opted for the single-PFAS model (i.e., the model that did not control for PFOA and PFOS) because the models fit well. Did the models that control for PFOA and PFOS not fit well? If not, then did this cause EPA concern over using this modeling data?
      i. We suggest making it explicit that EPA independently confirmed the modeling results from the Budtz-Jorgensen and Grandjean (2018b) paper, assuming that EPA did this. if EPA did not independently model this data, they should and they should make their assessments publicly available.
      ii. We suggest providing stronger support for opting for a 5% BMR rather than a 10% BMR.

7. Consistency in study evaluation: it seems at points that judgements around studies and outcomes are not fully transparent. For antibody levels, there were 3 studies in humans, 2 of which were in

the same population. The text states: “Although results were not always statistically significant, the general trend toward lower antibody levels was apparent.” The text further details some associations that were in the inverse direction of the others. This was concluded to be strong support of antibody alterations and is in fact the underlying study/endpoint for the final RfD. On the other hand, for endocrine effects, there are 9 studies in humans on thyroid hormones. The text indicates that these studies were inconsistent in the associations and imprecise (i.e., not statistically significant). Therefore, EPA concluded there was inadequate evidence to make a conclusion around endocrine effects in humans. These inconsistent and imprecise associations seem to be similar to the evidence for immune effects, but EPA came to substantially different conclusions around these bodies of evidence. A more transparent understanding of the overall conclusions drawn by EPA is warranted.

8. General comment on data gaps: Is EPA amenable to developing a table that summarizes all data gaps described throughout the assessment?

9. Section 4.3. CONCLUSIONS REGARDING SUSCEPTIBLE POPULATIONS AND LIFE STAGES (p 4-3) This section does not discuss the current understanding of the of the human health and environmental risks of PDFA as it relates to environmental justice and susceptible communities. This topic could be discussed in “Conclusions Regarding Susceptible Populations and Life Stages”.
    - Please provide insight on this topic as it relates to PDFA exposure or a rationale for not including such information.

10. Section 5.1. NONCANCER AND CANCER HEALTH EFFECT CATEGORIES CONSIDERED
    Page 5-2: “Given the lack of comprehensive subchronic or chronic animal studies, medium and high confidence short-term studies in animals of longer exposure duration (e.g., 28 days versus 7 or 14 days) and with exposure levels near the lower dose range of doses tested across the evidence base were preferred, along with medium or high confidence animal studies evaluating exposure periods relevant to developmental outcomes. These types of medium and high confidence human and animal studies increase the confidence in the resultant RfD because they represent data with low risk of bias and reduce the need for low-dose and exposure duration extrapolation (Appendix C, 22 Section 11.1).”
    - Please explain how these studies represent low risk of bias so the reader is clear on the assumptions here.

11. **“Evidence Suggests”** category

    a. Female reproductive toxicity - Page 3-158 – Wouldn’t the data integration for this endpoint fall into the “evidence suggests” category? Based on other evaluations that focused solely on strong animal data, it seems to us that “evidence suggests” would be consistent with how evidence integration was assessed in other assessments.

    b. EPA states that the evidence is inadequate to draw a conclusion for cardiometabolic effects, but the peer reviewer charge questions states that “evidence suggests” for cardiometabolic effects. Please correct one to ensure consistency between documents.

12. Selection of endpoints for the reference dose
    a. Page 5-32 and 5-42 – The developmental toxicity endpoints appear to have much greater correlation to clinically relevant adverse endpoints in humans compared to the immune endpoints used for reference dose characterization. Why were the immune toxicity endpoints preferred when the developmental toxicity endpoints had more robust data in terms of clinical relevance? Based on how the selection is described, one could conclude that EPA sought only the lowest reference dose, not the most relevant or robust reference dose. We do not believe this is the interpretation that EPA would like readers to take away and recommend greater discourse in the decision to use the immune data even though clinical relevance is clearer with the developmental toxicity data.

13. Figure 3-21: it is unclear why Lee, 2016 is considered critically deficient while Cao, 2018 (as an example) is considered deficient. The ratings across the domains are consistent with Lee even having a better rating in one domain. These figures should allow for transparent understanding of the evaluations for studies. It seems for Lee, 2016 that the confounding, selection, and sensitivity domains should have individually been considered critically deficient.

14. In the RfD derivation section, it says that the epi studies provided "moderate" evidence for developmental effects. No such qualification was provided for the immune effects section; instead this section begins with "… the strongest evidence." This language at the start compared to opening the developmental section with "moderate" seems to imply that the 2 immune effects epi studies are given more weight than the seventeen developmental epi studies. Please be consistent in interpretation of the bodies of evidence and the language used.

Minor Comments:

1. On page 3-1, it states that the elimination half-life of PFDA is 4.5-12 years – please provide a reference for this.

2. Page 3-109: It would be helpful for the gestational duration summary to indicate whether the evidence indicated duration was *increased* or *decreased*.

3. Page 3-143: "the masculinization programming window" – does this refer to prenatal programming or the early postnatal changes that occur in testes development in human male infants? Or maybe both? If both, recommend changing the word to "windows" and mention that there is more than one masculinization window. If early postnatal development of the testes is not considered part of a "programming window", can IRIS weigh in on whether effects in the early postnatal period in humans are also a possibility?

4. Page 3-152: It would be helpful to the reader for EPA to include the changes in day duration of the various estrous phases. For example "A significant trend test was observed for the percentage of time spent in estrus with statistically significant decreases (42-84%; X-X days) compared to controls (average of X days) at >/= to 1.25 mg/kg/d." Without reference to the duration it is difficult to translate the % change.