Agency for Toxic Substances and Disease Registry (ATSDR)
Comments on the Interagency Science Consultation (Step 3)
Draft IRIS Toxicological Review of Perfluorononanoic Acid (PFNA) and Related Salts
Dated July 2023
(Date Received August 25, 2023)

Executive Summary

- Suggest providing some environmental levels of PFNA in the ES
- "There was also no compelling evidence to suggest that confounding by other PFAS was responsible for the inverse associations in the sub-set of PFNA studies evaluating single and multi-PFAS models in relation to birth weight deficits." In our opinion, the strength of this statement is not warranted. While there is support that you are able to tease out the effects of PFNA, it is impossible to be completely sure that the effects are due to PFNA. More tempered language is recommended here.

Chapter 1

- 1.1.4. Suggest including more estimates of exposure in water. Are there any studies from states or other groups that you could include that would provide an estimate of actual exposure values rather than just detect/non-detect in UCMR?
    - Or can you provide some more quantifiable measures (e.g., median or mean, range) for the detects in UCMR? (similar to the level of detail provided in the other sections in 1.1.4
- PODhed = 1.9x10-7 mg/kg/day = 1.9x10-4 ug/kg/day → levels in NHANES around 0.6ug/kg/day
    - Is there any concern that the level being used for RfD derivation is 3 orders of magnitude lower than what is being seen on average in NHANES participants? With an additional 30 UF, wouldn't this suggest that all people would be born significantly below average birth weight?

Chapter 3

- Spontaneous abortion: do the biases in the medium confidence study also bias toward the null as EPA concluded the low confidence studies do? This section seems to weight the low confidence study more than the medium confidence study. Suggest being more neutral in discussing these results.
- Immunosuppression Human studies: EPA cites several references for specifying that antibody response is a well-accepted measure (i.e. WHO & IPCS. I2012. Guidance for immunotoxicity risk assessment for chemicals); however, WHO heavily caveated the clinical relevance of this effect for PFAS (WHO. 2022. PFOS and PFOA in Drinking-water: Background document for development of WHO Guidelines for Drinking-water Quality):

WHO 2022

- "In summary, it is suggested that decreased antibody response to vaccination may lead to reduced immune system functionality. However, studies report inconsistencies in the relationship between PFAS exposure and infection propensity in early life (Antoniou et al., 39 2022; ATSDR, 2021; EFSA, 2020; Steenland et al., 2020; US EPA, 2021a; 2021b) and therefore, the clinical relevance of these findings is unclear. More studies, particularly with more objective measures of infections, are needed (EFSA, 2020)."

Can EPA cite this and update language as appropriate around this and the significance of these effects given that WHO (one of the citations EPA uses to support this) heavily caveated the interpretation of these results?

- Faroe Island studies: EPA seems to treat all the Faroe Island studies as separate support for the antibody response, yet earlier in the assessment EPA makes the following comment:

> "The evaluations below also do not include two publications where similar results were already reported in included studies (i.e., referred to as overlapping publications here): (Woods et al., 2017) from the Health Outcomes and Measures of the Environment cohort (Shoaff et al., 2018), and (Rokoff et al., 2018) from the Project Viva cohort (Sagiv et al., 2018)." (section 3.3.2, page 3-38)

Why did EPA not treat the Faroe Island cohort studies in a similar way? Justification for the seeming inconsistency between these approaches should be provided. We understand these studies focus on different time periods in the children, but it still seems that the rationale used in section 3.3.2 would be relevant here as well.

- Immune Endpoints
  - ATSDR agrees with EPA's decision not to consider the 5% decrease (1/2 standard deviation) in vaccine antibody response for the derivation of PFNA RfDs; however, ATSDR disagrees with EPA's assessment of the clinical relevance of that endpoint. The literature suggests changes in IgG may only be clinically relevant if the magnitude of change is 2 standard deviations and changes are noted in more than one antibody (Agarwal and Cunningham-Rundles. 2007. Assessment and Clinical Interpretation of Reduced IgG Values). Although the WHO considers decreased vaccine antibody titers to be sufficient evidence for immunotoxicity (IPCS 2012), the WHO did not consider this endpoint for derivation of their health guidance values in their draft PFOA and PFOS assessment (WHO 2022). Recent PFAS evaluations/reports from ATSDR (2021), NASEM (2022), and WHO (draft, 2022) have not suggested an association between PFNA and/or PFAS exposure and risk of infection.
  - 3-94: Lines 9-12: "The decreases were generally large" The majority of antibody decreases were between 5 and 10%. In the case of antibody titers, in which there is already a wide range of normal values (Agarwal and Cunningham-Rundles 2007; Schauer et al. 2003. "Levels of antibodies specific to tetanus toxoid…"), 10% would still be considered minimal and not "generally large". Can EPA provide a citation supporting that these decreases are considered generally large?

Uncertainty Factors for RfDs

- Given the combined availability of candidate animal and epidemiological studies from PFNA and read-across data from other PFAS, ATSDR does not believe that an uncertainty factor of 3 for database limitations is needed.

BMD

- Although ATSDR still has concerns about PFAS confounding, the hybrid approach used for low birth weight BMR calculations is well described. It is great to see EPA using adversity cut-offs (babies born <2500g) and considering recent data (2018 rates of low-birth-weight births) when defining the BMR.
- The Scientific Advisory Board (2022) who evaluated the EPA OW assessments on PFOA and PFOS stated "the panel is not aware of evidence for associations of PFOA and PFOS with adverse consequences such as developmental delays in low birth weight/small for gestational age infants." Although their comment was focused on PFOA and PFOS, this is still relevant to PFNA. Suggest adding language to address this concern.

General

- The language used by EPA throughout the assessments is inconsistent. On lines 3-5 on page 3-243, EPA concludes "The available human epidemiological studies provide slight evidence of developmental neurotoxicity, with considerable uncertainty." In the charge questions, EPA words it such that "the available evidence suggests but is not sufficient to infer". ATSDR suggests EPA remain consistent throughout.
- Pg 1-15, lines 13-14 "When possible, results across studies are compared using graphs 13 and charts or other data visualization strategies." – it is not entirely clear how to draw conclusions from this.
- The evaluation of health effects has been inconsistent between reviews of different PFAS species across EPA. For instance, while this PFNA review considered thyroid effects relevant to human health, the draft for PFDA ATSDR reviewed in early 2022 did not.

ATSDR recommends EPA comment on the ability of current analytical methods to detect PFNA at the level of the draft RfDs