**Department of Defense (DoD)**
**Comments on the Interagency Science Consultation (Step 3)**
**Draft IRIS Toxicological Review of Perfluorononanoic Acid (PFNA) and Related Salts**
**Hepatic Effects Section and Modeling Results for Liver Toxicity**
**Dated December 2023**

*Comment categories: Science or methods (S); Editorial, grammar/spelling, clarifications needed (E); or Other (O). Also please indicate if Major i.e. affects the outcome, conclusions or implementation of the assessment.

| Section | Page (Lines) | Comment | Suggested Action | Category |
|---|---|---|---|---|
| **General** | - | Concerns remain regarding lack of mode of action/mechanism for understanding the developmental toxicity from exposure to PFNA. Effects observed in rodents (decreased postnatal survival, reduced postnatal body weight, developmental delays) are similar but not identical for humans (reduced birth weight). Optimally, mode of action/mechanistic data could be used (possibly with IVIVE) to provide corroboration for effects observed in controlled laboratory rodent studies if the same or similar biological pathways are conserved across species, as was done with PFNA and hepatic effects. No mode of action information is provided that supports the hazard assessment. | Please consider discussing evidence regarding mode of action/mechanism of action here as a way to further corroborate the effects. | S |
| **General** | - | Since this epidemiological report relied on serum/plasma biomarkers and hepatocellular injury, did authors consider PBPK modelling for human health risk assessment of PFNA? | For example, please see the following:<br><br>Exploring sex differences in human health risk assessment for PFNA and PFDA using a PBPK model. Kim SJ, Choi EJ, Choi GW, Lee YB, Cho HY. Arch Toxicol. 2019;93(2):311-330. doi: 10.1007/s00204-018-2365-y. Epub 2018 Nov 27. | S |

| Section | Page (Lines) | Comment | Suggested Action | Category |
|---|---|---|---|---|
| | | | And the following, which was a U.S. EPA co-authored work.<br><br>A Model Template Approach for Rapid Evaluation and Application of Physiologically Based Pharmacokinetic Models for Use in Human Health Risk Assessments: A Case Study on Per- and Polyfluoroalkyl Substances. Bernstein AS, Kapraun DF, Schlosser PM. Toxicol Sci. 2021;182(2):215-228. | |
| **General** | - | It seems authors may have leaned somewhat on the following reference:<br><br>"Exposure to per- and Polyfluoroalkyl Substances and Markers of Liver Injury: A Systematic Review and Meta-Analysis. Costello E, Rock S, Stratakis N, Eckel SP, Walker DI, Valvi D, Cserbik D, Jenkins T, Xanthakos SA, Kohli R, Sisley S, Vasiliou V, La Merrill MA, Rosen H, Conti DV, McConnell R, Chatzi L. Environ Health Perspect. 2022 Apr;130(4):46001." | The authors may consider citing this reference. | |
| **3.2.4 Human Studies** | 2 (11-23, 27) | Information provided in this section was unclear. Authors state 16 available studies were considered. Line 22, then reads "Nine of the informative studies were cross-sectional ……" How did authors arrive at 9 studies? What are those studies? Is this Figure 3-29 data? Line 27 – "the other cross-sectional studies ……..". Rather than state "the other", please state very clearly those study references for clarity. | Clearly indicate which studies are being referred to here. | E |

| Section | Page (Lines) | Comment | Suggested Action | Category |
|---|---|---|---|---|
| **3.2.4 Human Studies** | 2 (13-14, 17) | "…Elevation of these markers is an indication of potential liver injury…." AND lines 13 and 14: "Serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are considered reliable markers of hepatocellular function/injury". The two statements appear contradictory. "Potential liver injury" as compared with "reliable markers of function/injury." The former might imply low/medium confidence in risk from exposure; the latter would imply moderate to high confidence since on the one hand we have "potential injury" and on the other "reliable marker of injury." | Please resolve this or add further explanation | S |
| **3.2.4 Human Studies** | 2 (31-32) | "…which had concerns for selection bias…" How? What were the concerns? What were the selection biases precisely? | Please consider including these concerns and potential selection biases here. | S |
| **3.2.4 Human Studies** | 2 (34-35) | "…….the latter of which was considered low confidence due [to] concerns for potential confounding and 35 exposure misclassification….." why was this study considered low confidence? What were the confounding factors? | Please explain exposure misclassification – such as what was provided, as compared to what was expected? | S |
| **3.2.4 Human Studies** | 4 (24-38), 5 (1-5) | Concerns remain regarding the potential for confounding exposures nested within epidemiological studies, specifically concurrent exposures of PFNA with PFDA, but also other PFAS and other contaminants. This makes any solid interpretations regarding dose response relationships for safety difficult. The fact that PFNA was among the most influential of the PFAS in three of the five studies doesn't appear to outweigh the significance of the effect of PFOS noted by Liu *et al.* (2022). Given that it is difficult to disentangle these effects into discrete attributable agents, a strong justification is required. | Please consider a more in-depth look at the potential for confounding due to mixture exposures, which particularly makes the case for the effects being truly related to mainly PFNA. Mechanistic information would also be useful here. | S |