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
Hepatic Effects Section and Modeling Results for Liver Toxicity
Dated December 2023
(Date Received December 7, 2023)

Overall

ATSDR only received a copy of the updated hepatic effects section (section 3.2.4) and appendix D.1 "Modeling results for liver toxicity" to review. We are not able to comment on any edits to the rest of the document, including those related to adjustments in RfD pharmacokinetic calculations. Overall, this new draft of the hepatic section is much improved from the previous draft. ATSDR hopes EPA made similar improvements throughout the entire document.

Hepatic Effects

EPA does a good job discussing the new studies added to the hepatic effects section and addressing the epidemiological database. We appreciate EPA's nuanced discussion, specifically around NHANES studies not necessarily needing to be treated as separate studies: "because of the overlapping population with other NHANES studies, this paper was not considered a separate study" (page 2, lines 25-27). ATSDR was not given a copy of the rest of the assessment for this review, but we recommend that the Faroe Island cohort studies are treated in a similar way for the updated draft.

ATSDR commends EPA for the thorough discussion on confounding by co-occurring PFAS in the epidemiological evidence for liver effects. This was a great addition to the text. ATSDR agrees with EPA's conclusion that confounding is unlikely to explain the observed associations, but the discussion does not address how confounding concerns affect the ability to derive reliable toxicity values for individual PFAS. Because confounding by multiple PFAS could result in lower guidance values for individual PFAS, ATSDR recommends EPA address these concerns.

Regarding the Attanasio 2019 paper, EPA indicated the study provided "no clear rationale" for the sex-based difference in ALT and AST (page 4 line 15-17); however, this study proposed a potential mechanism mediated by HNF4α (paragraph 5 of the discussion; on page 7 if reading the PDF).

Modeling Results for Liver Toxicity

We recommend EPA discuss the appropriateness of using cross-sectional ALT data for the derivation of RfDs. Additionally, it's unclear why studies based on NHANES data, which were also cross-sectional in design, were not considered for derivation of RfDs. Additional rationale would strengthen this approach.