EPA PFHxA IRIS Assessment

ATSDR Comments

These comments follow the EPA EPR charge questions document in order to ensure all topics are addressed.

1. The SR protocol developed by EPA for PFBA, PFHxA, PFHxS, PFNA, and PFDA is appropriate and should adequately capture the relevant literature for PFHxA.
    a. Is Appendix A going to have the full SR protocol? or will it stay as is with just a paragraph and a link to the EPA landing page for the protocol? Either way is fine, but ATSDR suggests updating the language around Appendix A in the actual assessment as it suggests the readers can find the full protocol in Appendix A, not just a link to the protocol online. This is especially awkward when the text states that Section 1.2 briefly summarizes the protocol with full details in Appendix A, and Section 1.2 is so much longer than Appendix A.
    b. To help the users/ readers a summary should be presented to report key findings when search, screening and extracting the relevant literature for PFHxA. It will be more advantageous that the links to a full text. Also Figure 2-1 can include more details above this schema as well as about colors, bold and information to better stand alone
2. HAWC Review – access was not provided for this assessment to ATSDR reviewers, so no comments on the HAWC component of the assessment are provided. However, ATSDR is contemplating developing an MRL based on the same study as that used by EPA – Loveless et al. (2009) – so there are no major quality concerns from ATSDR for this study. A figure which summarizes the confidence for the studies will improve visibility. More insights between NTP 2018 study vs. Loveless et al. 2009 will improve the context of the supporting findings and to define the strengths and limitations when assigning confident.
3. Health Effects: why was read-across evidence not considered in the evaluation of PFHxA health effects? It seems like this was done for hepatic effects in regard to PPAR-alpha. The assessment notes that studies on other PFAS in PPAR-alpha-null mice support concluding that the hepatic effects are relevant to humans. However, for other potential health effects, evidence for structurally similar PFAS was not considered in EPA's evaluation. ATSDR recommends that EPA be consistent in applying read-across evidence in the evaluation of health effects.
    a. EPA does a good job integrating the evidence around hepatic effects and providing support for why these effects are considered relevant to humans.
    b. From Tableau, it looks like there are 3 developmental studies, but the Summary Section (Section 4.1) says that the conclusions for developmental effects are based on 2 studies. Please make sure this is correct.
    c. EPA's conclusions around the hematopoietic effects of PFHxA exposure are scientifically justified and clearly described.
    d. In general, EPA's conclusions around endocrine effects are scientifically justified and clearly described. EPA discusses the possibility that thyroid changes are secondary to hepatic effects. ATSDR also recommends EPA discuss other mechanisms by which PFAS may disrupt thyroid endpoints. For example, there is evidence PFAS species may bind to

thyroid hormone receptors. However, the evidence for PFHxA suggests this binding may be weak. ATSDR recommends EPA include an expanded suggestion around this to include the following references:

i. Structure-activity relations in binding of perfluoroalkyl compounds to human thyroid hormone T3 receptor - PubMed (nih.gov)
ii. Binding interactions of perfluoroalkyl substances with thyroid hormone transport proteins and potential toxicological implications - PubMed (nih.gov)
iii. A hypothesis-driven weight-of-evidence analysis to evaluate potential endocrine activity of perfluorohexanoic acid - PubMed (nih.gov)

e. ATSDR agrees with EPA's conclusions around the other potential health effects discussed in this assessment.
    i. It might be good to include a data needs section at the end of Section 3 that summarizes the gaps in literature for assessing these effects.
    ii. EPA indicates evaluation of effects on the immune system are "limited to changes in structural components…which are less predictive indicators of immunotoxicity" (3-96). ATSDR suggests EPA discuss immune effects of other PFAS species here (see above about read-across), particularly those that have identified changes in immune function, to strengthen the evidence for immune effects and call for additional studies "particularly those that evaluate changes in immune function…"

4. ATSDR supports EPA's conclusions around hepatic effects and PPAR-alpha. There is uncertainty around these effects for all PFAS due to PPAR considerations. EPA is being conservative and protective of human health by considering these effects relevant, as many of the hepatic effects across PFAS-species are found at the low doses.
    a. EPA indicates evidence that PFHxA is a more potent activator of human than mouse PPARα based on the LOEC values (3-32); however, the authors in the study (Wolf et al. 2008) conclude mouse PPARα to be more sensitive to PFHxA than human PPARα. They base this conclusion by adjusting the outcome to a percentage of maximal response as a way to more directly compare responses. When this was completed, the concentration to elicit 20% of maximal response was 38 µM in mouse and 47 µM in humans. Why did EPA choose to focus on the LOEC values over the relative responses?
        i. On 3-35, Wolf et al. (2014) is cited for human>rodent activation; however, Wolf et al. (2014) solely focused on mouse PPARα. Was Wolf et al. (2012) the intended citation? The authors in Wolf et al. (2012) reached a similar conclusion in the study as Wolf et al. (2008) regarding mouse versus human PPARα activation.
    b. From 3-33 (Consideration for Potentially Adaptive Versus Adverse Responses): "Evidence also showed increased PPARα activation and peroxisomal beta oxidation after PFHxA exposure…that are possibly biological pathways towards hepatocellular hypertrophy…" The shorter-term studies observed increased hepatocellular hypertrophy that was not observed in the Klaunig study. ATSDR suggests EPA re-emphasize the Klaunig et al., 2015 study utilized PFHxA doses 2-10 x lower than the shorter-term studies, similar to how this was indicated in the histopathology section (3-21).

5. ATSDR agrees with the conclusions around carcinogenicity of PFHxA because there is insufficient evidence investigating this (only 1 animal study).
6. ATSDR supports the use of the Loveless et al. 2009 study for RfD derivation. This is a strong study that provides evidence for developmental effects at low levels. The selection of this study and endpoint is well-supported by EPA. It would be good to include a statement about the translation of clinical evidence in animals to human health outcomes at these low levels, as well as strengths and limitations when compared with NTP study.
7. See above.
8. Overall, ATSDR supports EPA's use of BMD. Modeling approaches are sufficient, including the use of endpoint specific BMRs (this is recommended, and EPA sufficiently justifies each BMR used). It is good to see that EPA has updated their BMD analysis to the newest version of BMDS (v3.2). The model selection is consistent across the studies/endpoints, and the models chosen seem appropriate (e.g., the visual fit looks good across modeling results).
9. EPA did a very thorough job discussing the toxicokinetic differences. There are options provided at multiple steps with justifications as to why those are appropriate or not. Based on the discussion, ATSDR feels that the ratio of CLs is appropriate for estimating HEDs. The rationale for using the female rat rather than a combined/average value for the Loveless et al. 2009 makes sense (i.e., that exposures were to dams and assumed equal clearance in a developing offspring as an adult).
10. ATSDR supports the UFs applied by EPA for the derivation of candidate RfDs. The use of a 3 for the interspecies UF is warranted and clearly justified by EPA.
11. ATSDR agrees with EPA's conclusion that there is not enough data to evaluate carcinogenicity of PFHxA. This conclusion is scientifically justified and adequately described.