

Food and Drug Administration (FDA)
Comments on the Interagency Science Discussion
Draft IRIS Toxicological Review of Perfluorohexanoic Acid (PFHxA) and Related Salts
February 2023
(Date Received March 2023)

As highlighted by a previous reviewer, we share concerns over the 6~7-fold lower value of the subchronic osRfD compared to the chronic osRfD for hematological effects, which seems illogical and potentially misleading. As the EPA has already noted in their response to the external reviewer's comment (page E-27 of the supplemental document), we suggest that the confidence level for the subchronic osRfD be lowered from medium-low to low. In addition, we recommend that the confidence level for the chronic osRfD also be reconsidered and lowered from medium to medium-low based on data from Klaunig et al. (2015). The study found that decreased red blood cells and hemoglobin levels occurred only at the highest dose tested and at one time point (51 study week, not 25 or 104 study week), indicating a lack of dose-response and time concordance for these effects. This suggests that the evidence for hematological effects may be weaker than initially thought, and warrants a re-evaluation of the confidence level.

Minor specific comments:

1. Both $T_{1/2}$ and $T_{0.5}$ have been used to represent half-life. Similarly, $BW^{3/4}$ and $BW^{0.75}$ have been used for scaling/dosimetric extrapolation. Please revise for consistency.
2. Page xvi: delete “300 based” in “endocrine UFC = 300 based~~300 based~~ on UFA = 3...” in footnote “e” on the bottom.
3. Page 1-10, lines 4~6 under 1.2.1: the final ATSDR assessment of PFAS was released in May 2021. This may be updated accordingly.
4. Page 1-5, line 26 under 1.2.5: delete “aa”
5. Page 2-1, line 7: “2323” should be “23”
6. Page 2-3, line 33: missing information or typo on “(i.e., s)”
7. Page 3-2, lines 13~14: it is not clear whether the “increase in clearance” is referring to male rats or female rats.
8. Page 3-19, line 7: Please check the hyperlink for “HAWC” is correct.
9. Page 3-24, line 2: n=99/10 should be n=9/10.
10. Page 3-24, line 5~16: Please specify the dose levels (or treatment groups) when making the comparisons. Please also check for the correctness of the numbers. E.g., in line 16 in “females (n = 8/70 vs. 11/60 in controls)”, n=8/70 refers to incidence for congestion in highest dose group in female rats, while 11/60 is actually the incidence in the low dose group (5 mg/kg-day) instead of “in controls” as it is presently written. The incidence should be 6/60 according to Klaunig et al., 2015. For clarity, it may be helpful to add a table for necrosis and congestion similar to the one used for hepatocellular hypertrophy findings.
11. Page 3-36, line 20: delete “PPAR” in “...involved in PPAR~~PPAR~~ signaling pathways”
12. Page 3-38, line 17: delete “Specifically.”
13. Page 3-39, line 12: “200 2mg/kg-day” should be “200 mg/kg-day”
14. Page 3-40, line 2: duplicate footnote, delete footnote 6 in the text and the linked content on the bottom of the page.
15. Page 3-44, line 5: “socio economic status” should be “socioeconomic status”
16. Page 3-52, line 7: delete “=”
17. Page 3-68, lines 1~3: check the accuracy of statement. It appears that the Klaunig et al., 2015 study did not report any significant hematological findings at 100 mg/kg-day in male rats at both 25 and 51 weeks.
18. Page 3-72, line 8: “decreased” should be “increased”
19. Page 3-75, line 21: “decreased” should be “increased”
20. Page 3-88, Table 3-29: NN/A should be N/A. This was seen multiple sites.
21. Page 3-104, Table 3-33: delete one “N/A (indeterminate animal evidence)”
22. Page 3-106, line 2: delete “immune” in “Asthma, ~~Immune~~, Immune Markers, and Potentially Related Respiratory Outcomes”
23. Page 4-1, 3rd paragraph under 4.1. Summary of Conclusion for Noncancer Health Effects: delete “differences.” in the sentence “...or other study design differences. ~~differences~~. Interestingly, necrosis was observed...”
24. Table 4-1. Footnote a and b: “ND = no data available for this outcome for this PFAS~~PFAS~~.”

25. Page 5-4, line 2: “ono” should be “on”
26. Page 5-8, Table 5.1: In the “Decreased red blood cells” entry/row, the effect was only observed in female rats (instead of both) under the “Strain, species, sex” column.
27. Page 5-8, Table 5.1: “Decreased, perinatal mortality” should be “Increased, perinatal mortality”
28. Page 5-13, line 9: “toxicokinetic information available ~~information available~~ for...”; line 12, “TKT data” should be “TK data”
29. Page 5-21, Table 5-5: a number of typos in the table in particular the “POD (mg/kg-d)” column and POD_{HED} column. Also check the Table 5-10 on page 5-32 for typos.
30. Page 5-23, line 17. Of those, the lowest POD_{HED} ~~POD_{HED}~~.