

National Institute for Occupational Safety and Health (NIOSH)
Comments on the Interagency Science Discussion
Draft IRIS Toxicological Review of Perfluorohexanoic Acid (PFHxA) and Related Salts
February 2023
(Date Received March 6, 2023)

Comments on Chapter 1: Overview of Background Information and Assessment Methods

Pages 1-2, 1-5 to 1-7, and the Reference section: Please update all the ATSDR 2018 citations to the most up-to-date ATSDR reference published in its final form (ATSDR 2021). Note that the link supplied under ATSDR 2018 in the References section goes directly to the 2021 final report.

Page 1-4, Table 1-1 Physicochemical properties of PFHxA: 1) The molecular formula for PFHxA is repeated in the table. 2) This comment also relates to a comment from Section E.6.1. Additional External Peer Review Comments, page E-29 of the Supplemental Information document. The reviewer noted that differences in values of water solubility and bioconcentration factor between the ammonium and sodium salts did not seem realistic. In response, the EPA added text to distinguish experimental and predicted values and to note that the predicted values may be less reliable. The additional comments here are of the same nature and perhaps the only response can be that the predicted values are less reliable. Nevertheless, it may be useful to point out where those predicted values appear erroneous. In addition to the water solubilities of the salts, as has already been noted, the vapor pressures of the salts should not be similar to or exceed the vapor pressure of PFHxA. Likewise, the boiling points of the salts should be much higher than that of the PFHxA.

Page 1-5, lines 3-5: Suggest adding or incorporating this sentence: “PFHxA has been detected as a breakdown product of PFAS used in water- and stain-protective coatings for carpets, paper, and textiles including textiles used in some protective clothing [Klaunig et al. 2015].” The use of PFAS in protective clothing is of particular interest as the compounds *may* be protecting from one hazard while introducing another, potentially making its elimination from these textiles more challenging than textiles used for recreation or sports performance. We do not yet know if it is a contributing source, but the title of section 1.1.2 includes “Use” and its application to protective clothing has different implications than its use for other textiles.

Page 1-5, lines 7-8: Suggest adding this sentence: “PFAS also have been used in aqueous film-forming foam (AFFF) for suppression of liquid fuel fires [Laitinen et al. 2014].” This text is important, because the reader may misinterpret it as being in all fire suppression products. Additionally, PFAS are the active constituents in AFFF and intentionally placed in foams to provide a barrier between oxygen and the liquid fuel source to suppress ignition. Lastly, it is important that the reader understand that alternative products must meet performance specifications related to liquid fuel fires instead of fires in only the built environment as a fuel source.

Page 1-5, lines 5-14: Suggest expanding the overview of sources, production, and use that contain PFAS across multiple occupational sectors and/or products including wood particle

board, rubber insulation, electroplating, metal treatments, paints, varnishes, and flame retardants [Glüge et al. 2020; OECD 2022].

Comments on Chapter 3: Pharmacokinetics, Evidence Synthesis, and Evidence Integration

Page 3-19, line 22: “There’re” should be deleted and sentence should read “Epidemiological studies report...”

Page 3-19, lines 25-27: “There was no consideration of potential confounding in the study design and analysis, including potential confounding by age, alcohol consumption, medical history, and socioeconomic status.” Age is an important confounder, but alcohol consumption, medical history, and socioeconomic status are more likely predictors of the outcome, not exposure, and therefore unlikely or weak confounders. Suggest rewording sentence to “There was no consideration of age in the study design or analysis, which is a relevant confounder of the association between PFHxA exposure and liver enzymes.”

Pages 3-20, line 2 and 3-55, line 13 use the phrase “exposure contrast.” Please briefly clarify the meaning of this phrase.

Page 3-44, lines 1-6: How is socioeconomic status predictive of PFHxA exposure in the study population? This would be needed to determine if it is an important confounder.

Page 3-55, line 5: How is socioeconomic status predictive of PFHxA exposure in the study population? This would be needed to determine if it is an important confounder.

Page 3-66, lines 10-15: How are socioeconomic status and medical history predictive of PFHxA exposure in the study population? This would be needed to determine if it is an important confounder. Neither medical history nor socioeconomic status are defined, and the rationale for their conceptualization as important confounders is missing, yet they are used as important benchmarks for the evaluation of confounding in almost every outcome evaluated. This requires additional explanation.

Pages 3-79, lines 5-7: The authors contend that medical history and socioeconomic status are important confounders of the association between PFHxA exposure and thyroid hormones. No explanations are provided about how these factors affect the exposure and outcome. Recommend discussing only age and sex as important confounders or add a specific explanation about why medical history and socioeconomic status are important confounders.

General comment: Previously, a reviewer commented that “while the interpretation of both epidemiologic studies is reasonable, it is not clear why the potential for confounding is considered to be so substantial without some indication of the rationale for expecting that serum PFHxA levels are associated with the confounding factors.” (from page E-11) This reviewer agrees with the comment, and it relates to the comments above. Each potential confounder should be clearly justified in its relationship to exposure and outcome.

References mentioned in comments above and not cited in the main draft document

Glüge J, Scheringer M, Cousins IT, DeWitt JC, Goldenman G, Herzke D, Lohmann R, Ng CA, Trier X, Wang Z [2020]. An overview of the uses of per- and polyfluoroalkyl substances (PFAS). *Environ Sci Processes Impacts* 22(12):2345–2373, <https://doi.org/10.1039/d0em00291g>. PMID: 33125022.

Laitinen, JA, Koponen J, Koikkalainen J, Kiviranta H [2014]. Firefighters' exposure to perfluoroalkyl acids and 2-butoxyethanol present in firefighting foams. *Toxicol Lett* 231:227–232, <http://dx.doi.org/10.1016/j.toxlet.2014.09.007>.

OECD [2022]. Per- and Polyfluoroalkyl substances and alternatives in coatings, paints and varnishes (CPVs), Report on the commercial availability and current uses. OECD Series on Risk Management, No. 70, Environment, Health and Safety, Environment Directorate, OECD, <https://www.oecd.org/chemicalsafety/portal-perfluorinated-chemicals/per-and-polyfluoroalkyl-substances-alternatives-in-coatings-paints-varnishes.pdf>.