National Institute for Occupational Safety and Health (NIOSH)
Comments on the Interagency Science Consultation Draft
IRIS Assessment of Perfluorobutanoic Acid (PFBA)
and Related Compound Ammonium Perfluorobutanoic Acid
August 2020
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[Comments received via email. Substantiative comments summarized in EPA's Response to Selected Interagency Comments on the EPA IRIS Website]

Comments from the National Institute for Occupational Safety and Health (NIOSH) on the Environmental Protection Agency (EPA) IRIS Toxicological Review of Perfluorobutanoic Acid and Related Compound Ammonium Perfluorobutanoic Acid

dated August 2020, EPA/635/R-20/131a, Interagency Review Draft (119 pages)

and Supplemental information—Appendix A, IRIS Assessments Protocol, updated February 2020 (203 pages)

September 9, 2020

Overall, the toxicological review document was clear, the methods were transparent, and the conclusions well supported.

Specific comments:

Page x: NIOSH is the National Institute **for** Occupational Safety and Health. Please change "of" to "for."

Page 3-5, line 30: EPA uses 70 kilograms (kg) as the standard species body weight (BW) here, but the EPA exposure handbook uses 80 kg as standard human BW now. Please explain why a different value is used here (or adjust).

Page 3-5: The discussion of $BW^{0.75}$ and why it is not used further is, for the most part, clear and transparent. However, the statement, "$BW^{0.75}$ scaling is not understood to be based on data for this class of chemicals" could benefit from additional explanation. Has this been shown for other perfluoroalkyls? Other evidence? In addition, since the male rats' values were within a factor of two of the human values, is there reason to believe that there may be something unique about the female rats and could an argument be made that the risks could be extrapolated based on $BW^{0.75}$ based on male rat data alone?

Page 3-6, line 13: Missing "n" on "know."

Page 3-12, caption for Figure 3-3: Should be "rationale."

Page 3-27 to 3-30: Excellent description of the evidence surrounding peroxisome proliferation and non-peroxisome proliferation modes of action as a cause of liver hypertrophy and other hepatic effects. This discussion is especially useful, given the conflicting, confusing array of in vitro and in vivo data. Well-reasoned conclusions are made regarding the adversity of the observed hepatic effects.

Page 5-5, Table 5-2: This table of benchmark response levels and the rationales for selection is highly informative and substantially enhances the transparency of the benchmark dose modeling. Nicely done.

Pages 5-6 to 5-7: Discussion of the dosimetric adjustment factor (DAF) based on clearance rates. This ratio is predicated on the idea that clearance is in the linear range. In the toxicokinetics section of the document, EPA discussed the possibility of a biphasic clearance. How would this impact the DAF calculation? A sentence or two explaining either the uncertainties because of this or how it is not an issue because of other factors would be helpful.

Page 5-8: Discussion of the $BW^{0.75}$ extrapolation factor. As noted above, additional clarification of why this factor is not relevant would be helpful.

Appendix A, page 2-3, lines 3—8: "*The chemical structures of PFDA, PFNA, PFHxA, PFHxS, and PFBA, and their related salts are shown in Figure 2-1 (along with their CASRNs), and estimated or experimental values for their physiochemical properties are provided in Table 2-1. Importantly, these values are intended for general context and may no longer be accurate or current at the time of review and should not be used for any purpose other than conveying generalities around physicochemical properties.*"

This is a point well taken. Nevertheless, it should be pointed out that the calculated/estimated values for boiling points of salts are similar to or lower than their corresponding free acids. Salts should have much higher boiling points than their corresponding free acids, if they do not decompose before boiling. To use a perfluoro compound as an example, the boiling point of trifluoroacetic acid is 72 degrees C. By comparison, the *melting point* of sodium trifluoroacetate is 207 degrees C and it decomposes before it boils.

Appendix A, page 2-4, Figure 2.1: The chemical structure of perfluorobutanoic acid, ammonium salt is incorrect. The ammonia is incorrectly bound to the carbon chain. The structure should be analogous to that of PFHxA.

Appendix A, page 2-4, Table 2-1: The table leaves as "ND" all the values associated with PFBA ammonium salt. However, the molecular weight is known and should be entered.

Appendix A, page 2-5, Table 2-1: Analogous to the previous comment regarding boiling point, the vapor pressures of the salts given in Table 2-1 are very similar to those of their corresponding free acids. The vapor pressures of the salts should be much lower than the corresponding free acids.

Appendix A, page 2-5, Table 2-1: The predicted pKa of PFHxS given as 0.14 is almost certainly highly inaccurate. This value is taken from a 2015 ATSDR document that references "SPARC 2008." Sulfonic acids as a class are much more acidic than their carboxylic acid analogs. For example, the pKa of acetic acid is 4.8. In contrast, the pKa of methanesulfonic acid is -1.9, almost 7 orders of magnitude more acidic. PubChem gives an estimated pKa for perfluoro*butane*sulfonic acid of -3.3. Perfluorohexanesulfonic acid and perfluorobutanesulfonic acid should have very similar pKa values. The significance of this is that the pKa value has a major influence on the compound's volatility, the partitioning between water and air, and the airborne phase in which the compound is likely to be encountered (i.e., vapor or aerosol). The value in the table of 0.14 suggests comparability between the

perfluorocarboxylic acids and the perfluorosulfonic acids and more similar distribution in the environment.