National Institute for Occupational Safety and Health (NIOSH)
Comments on the Interagency Science Consultation
Draft IRIS Toxicological Review of Perfluorodecanoic Acid (PFDA)
March 2022
(Date Received April 12, 2022)

[These comments included the attachment of five studies.]

The draft document is well written with rich information and useful summaries and tables. Our comments address the physical and chemical properties and new publications that could be added to Chapter 3, Pharmacokinetics, Evidence Synthesis, and Integration.

Comments on physical and chemical properties

Page xiii: "PFHxA" is used instead of "PFDA"

Page 1-2, Figure 1-1: The image for PFDA sodium salt is backwards and needs to be flipped 180 degrees.

Page 1-3, Table 1-1: The physical-chemical property values of PFDA generally do not match those in the CompTox Chemicals Dashboard or the 2021 update of Systematic Review Protocol for the 5 PFAS compounds. The values for the PFDA ammonium and sodium salts also do not match those in the CompTox Chemicals Dashboard or the 2021 update of Systematic Review Protocol for the 5 PFAS compounds. However, the values for the salts in the Dashboard and 2021 Systematic Review do match each other. Presumably the values in the Dashboard are frequently updated. The PFDA Toxicological Review does contain values consistent with the 2019 version of the Systematic Review.

Page 1-3, Table 1-1: Vapor pressure. The vapor pressure of PFDA in the 2021 update of the Systematic Review matches the value in Smith et al. [2016] (1.5 x 10-3 mm Hg). However, the vapor pressures for PFDA and its salts in Figure 1-1 are different than those in the CompTox Chemicals Dashboard and the 2021 update of Systematic Review Protocol for the 5 PFAS compounds. That said, the differences are relatively small between those sources. Of greater significance is that there is also only a small difference between the vapor pressure of PFDA and its salts. It is normal for carboxylic acids and their salts to have dramatically different vapor pressures. There is much more literature data on PFOA and its salts than for PFDA and its salts. A comparison of the vapor pressures of PFOA and its salts can serve as a model for the expected differences between PFDA and its salts. Barton et al. [2007] reported a vapor pressure for PFOA of 1.65 x 10-2 mm Hg, but 6 x 10-5 mm Hg for the PFOA ammonium salt. This PFDA Toxicological Review gives very similar values for PFDA and its salts. The dashboard and 2021 Systematic review do give about an order of magnitude difference between PFDA and salts, but a much smaller difference than Barton et al. [2007].

Page 1-3, Table 1-1: Water solubility. Table 1-1 gives a very low water solubility for PFDA (8.3 x 10-6 M). Smith et al. [2016] give the PFDA water solubility as 0.018 M and Kaiser et al. give it as 5 x 10-4 M. Because of the limited literature data related to PFDA and its salts, it is again

useful to compare existing data on PFOA and its salts. It is a common theme in the literature for the solubility of PFOA to be dependent on its state of ionization (Smith et al. [2016], Barton et al. [2007], Kaiser et al. [2006], Buck et al. [2011], Prevedouros et al. [2006]). The ammonium and sodium salts have relatively high solubility owing to their inherent ionized state. The solubility of PFOA at very low pH is estimated to be very low by Barton et al. [2007] (1.7 x 10-6 M), but this publication refers to the perfluorooctanoate anion as highly soluble at neutral and higher pH. Because the perfluoroalkanoic acids are such strong acids, they will be almost completely ionized in all but the most extremely acidic water solutions. Therefore, it would be expected that the solubility of PFDA in water of moderate pH would more greatly resemble that of its salts. The pH dependence of the solubility of the perfluoroalkanoic acids may contribute to the wide range of solubilities in the literature.

A quote from page 520 of Buck et al. [2011] (cited in the EPA PFDA draft tox review on page 1-1) addresses the important differences between vapor pressures of perfluoroalkanoic acids and their salts and well as the differences in solubilities between un-ionized acids and their anions: "The protonated and anionic forms have very different physicochemical properties. For instance, the perfluorooctanoate anion is highly water-soluble and has negligible vapor pressure, whereas perfluorooctanoic acid has very low water solubility and sufficient vapor pressure to partition out of water into air…".

Recent publications to consider for Chapter 3

For section 3.1.2 Distribution, Human (begins on page 3-5): Lind et al. [2022] reported that "…PFOA, and especially PFNA and PFDA were inversely related to multiple measures reflecting the amount of fat, but in women only."

For section 3.2 Noncancer Health Effects (begins on page 3-19): Truong et al. [2022] reported developmental (neuro)toxicity of diverse PFAS including perfluorodecanoic acid (PFDA) in a zebrafish model. The study found that of the 139 structurally diverse PFAS, 49 (35%) induced either abnormal morphology, embryonic and larval photomotor response or a combination as determined by benchmark dose analysis. The most potent PFAS found was PFDA.

For sections 3.2.1/3.2.2: Li et al. [2022] reported global changes in gene expression in the liver of PFDA-treated mice using microarray analysis. The results suggested that one of the main toxic effects of PFDA in the treated mice was the inhibition of immune response.

For section 3.2.8, Cardiometabolic Effects (begins on page 3-194): Dunder et al. [2022] concluded that "In this longitudinal study with three measurements over 10 years of both plasma PFAS and lipids, changes in six out of the eight investigated PFAS were positively associated with changes in plasma lipids, giving further support for a role of PFAS exposure in human lipid metabolism." They also stated: "For example, changes in perfluorodecanoic acid (PFDA) were positively associated with the changes in total cholesterol (β: 0.23, 95% confidence interval (CI): 0.14 to 0.32), triglycerides (β: 0.08, 95% CI: 0.04-0.12) and HDL-cholesterol (β: 0.08, 95% CI: 0.04-0.11)."

For section 3.3.1, Cancer - Mechanistic studies and supplemental information (begins on page 3-226): Zhang et al. [2019] reported that PFDA may suppress cellular senescence induced by p53 through the regulation of cIAP2 protein expression.

References (Copies of references marked with an asterisk will be sent with our comments.)

*Barton CA, Kaiser MA, Russell MH [2007]. Partitioning and removal of perfluorooctanoate during rain events: the importance of physical-chemical properties. J Environ Monit *9*:839–846.

Buck RC, Franklin J, Berger U, Conder JM, Cousins IT, de Voogt P, Jensen AA, Kannan K, Mabury SA, van Leeuwen SP [2011]. Perfluoroalkyl and polyfluoroalkyl substances in the environment: terminology, classification, and origins. Integr Environ Assess Manag *7*(4):513–541, http://dx.doi.org/10.1002/ieam.258.

Dunder L, Lind PM, Salihovic S, Stubleski J, Kärrman A, Lind L [2022]. Changes in plasma levels of per- and polyfluoroalkyl substances (PFAS) are associated with changes in plasma lipids - A longitudinal study over 10 years. Environ Res *211*:112903, https://doi.org/10.1016/j.envres.2022.112903.

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*Li K, Zhao Q, Fan Z, Jia S, Liu Q, Liu F, Liu S [2022]. The toxicity of perfluorodecanoic acid is mainly manifested as a deflected immune function. Mol Biol Rep, published online March 2, 2022, https://dx.doi.org/10.1007/s11033-022-07272-w.

Lind PM, Lind L, Salihovic S, Ahlström H, Michaelsson K, Kullberg J, Strand R [2022]. Serum levels of perfluoroalkyl substances (PFAS) and body composition–A cross-sectional study in a middle-aged population. Environ Res *209*:112677, https://dx.doi.org/10.1016/j.envres.2022.112677.

*Prevedouros K, Cousins IT, Buck RC, Korzeniowski SH [2006]. Sources, fate and transport of perfluorocarboxylates. Environ Sci Technol *40*(1):32–44.

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Truong L, Rericha Y, Thunga P, Marvel S, Wallis D, Simonich MT, Field JA, Cao D, Reif DM, Tanguay RL [2022]. Systematic developmental toxicity assessment of a structurally diverse library of PFAS in zebrafish. J Hazard Mater *431*:128615, https://dx.doi.org/10.1016/j.jhazmat.2022.128615.

Zhang Z, Song N, Peng Y, Fan Z, Han M, Zhao M, Dong T, Liu S [2019]. Evironmental (sic) pollutant perfluorodecanoic acid upregulates cIAP2 to suppress gastric cell senescence. Oncol Rep *41*(2):981–988, https://doi.org/10.3892/or.2018.6856.