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IRIS Toxicological Review of Perfluorohexanesulfonic Acid (PFHxS, CASRN 335-46-4) and Related Salts

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EXECUTIVE SUMMARY

Perfluorohexanesulfonic acid (PFHxS, CASRN 355-46-4),[1] and its related salts (such as potassium perfluorohexanesulfonate [PFHxS-K, CASRN 3871-99-6], ammonium perfluorohexanesulfonate [PFHxS-NH_4, CASRN 68259-08-5], and sodium perfluorohexanesulfonate [PFHxS-Na, CASRN 82382-12-5]), are members of the group per- and polyfluoroalkyl substances (PFAS). This assessment applies to PFHxS as well as nonmetal and alkali metal salts of PFHxS that would be expected to fully dissociate in aqueous solutions of pH ranging from 4 to 9 (e.g., in the human body) and not release other moieties that would cause toxicity independent of PFHxS. The synthesis of evidence and toxicity value derivation presented in this assessment focuses on the free acid of PFHxS and its potassium, sodium, and ammonium salts given the currently available toxicity data.

Concerns about PFHxS and other PFAS stem from the resistance of these compounds to hydrolysis, photolysis, and biodegradation, which leads to their persistence in the environment. PFAS are not naturally occurring; they are manmade compounds that have been used widely over the past several decades in industrial applications and consumer products as many PFAS are resistant to heat and are used to confer resistance of products (e.g., textiles) to stains by repelling oil, grease, and water. PFAS are also used in a wide range of other applications, including electrical insulation and to confer frictionless coatings onto surfaces. PFAS in the environment are found at industrial sites, military fire training areas, wastewater treatment plants, and in commercial products (see Appendix A, Section 2.1.2).

The Integrated Risk Information System (IRIS) Program is developing a series of five PFAS assessments (i.e., perfluorohexane sulfonate [PFHxS], perfluorobutanoic acid [PFBA], perfluorohexanoic acid [PFHxA], perfluorononanoic acid [PFNA], perfluorodecanoic acid [PFDA], and their associated salts) (see December 2018 IRIS Program Outlook) at the request of EPA national programs and regions. Specifically, the development of human health toxicity assessments for exposure to these individual PFAS represents only one component of the broader PFAS strategic roadmap at the EPA (https://www.epa.gov/pfas/pfas-strategic-roadmap-epas-commitments-action-2021-2024). The systematic review protocol (see Appendix A) for these five PFAS assessments outlines the related scoping and problem-formulation efforts, including a summary of other federal and state assessments of PFHxS. The protocol also describes the systematic review and dose-

[1] The CASRN given here is for linear PFHxS; the source of PFHxS used in toxicity studies was reported to be 98% pure and reagent grade, generally giving this CASRN. None of the studies referenced in this assessment explicitly state that only the linear form was used. Therefore, there is the possibility that a minor proportion of the PFHxS used in the studies were branched isomers and thus observed health effects may apply to the total linear and branched isomers in a given exposure source.

response methods used to conduct this review (see also Section 1.2). In addition to these ongoing IRIS PFAS toxicity assessments, EPA's Office of Research and Development is carrying out several other activities related to PFAS, including the creation of PFAS systematic evidence maps (SEMs) (Shirke et al., 2024; Radke et al., 2022; Carlson et al., 2022) and consolidating and updating PFAS data on chemical and physical properties, human health toxicity, and pharmacokinetics, as well as ecotoxicity.

Human epidemiological studies have examined possible associations between PFHxS exposure and health outcomes, including immune responses, birth weight, hematopoietic effects, thyroid hormone effects, liver enzyme effects, serum lipids effects, cardiovascular disease, hematological effects, reproductive effects, neurodevelopmental effects, and cancer. The ability to draw conclusions from the epidemiological evidence for the assessed health outcomes is limited (apart from immune effects) by the overall quality and lack of consistency in the available studies.

Animal studies of PFHxS exposure exclusively examined the oral exposure route; therefore, no inhalation assessment was conducted nor was an inhalation reference concentration (RfC) derived (see Section 5.2.3). The available animal studies of oral PFHxS exposure examined a variety of noncancer endpoints, including those relevant to the thyroid, immune system, developmental effects, hematopoietic system, hepatic effects, cardiometabolic effects, reproductive (male and female) system, nervous system, and renal effects. Some limitations in the animal database include the types of studies identified (e.g., few subchronic studies and no chronic exposure studies were available), and few studies per health outcome.

Overall, the available **evidence indicates** that PFHxS exposure is likely to cause thyroid and developmental immune effects in humans, given sufficient exposure conditions. For thyroid effects, the primary supporting evidence for this hazard conclusion included evidence of decreased thyroid hormone levels, abnormal histopathology results, and changes in organ weight in experimental animals. For immune effects, the primary supporting evidence included decreased antibody responses to vaccination against tetanus or diphtheria in children. Selected quantitative data from these identified hazards were used to derive toxicity values (see Table ES-1; see Sections 3.2.1 and 3.2.2 for evidence synthesis and integration analyses).

Evidence primarily from epidemiological studies **suggests** but is insufficient to infer that PFHxS exposure might affect fetal development, specifically resulting in decreased birth weight (see Section 3.2.3). However, because of limitations and uncertainties in the currently available studies, a hazard could not be clearly identified, and these data were not considered for use in deriving toxicity values. While no reference dose (RfD) was derived for developmental effects, a point of departure (POD) was derived and presented for comparison purposes (see Section 5.2.1).

Evidence from epidemiological and animal studies **suggests** but is insufficient to infer that PFHxS exposure may cause hepatic effects, specifically increases in serum biomarkers (see section 3.2.4). However, because of limitations and uncertainties in the currently available studies, a hazard could not be clearly identified, and these data were not considered for use in deriving toxicity values.

While no reference dose (RfD) was derived for hepatic effects, a POD was derived and presented for comparison purposes (see Section 5.2.1).

In addition, evidence from human and animal studies **suggests** but is insufficient to infer that PFHxS exposure may cause neurodevelopmental and cardiometabolic effects in humans.

Lastly, although evidence from humans and or animals was also identified for hematopoietic, reproductive, renal, and carcinogenic effects, the currently available **evidence is inadequate** to assess whether PFHxS exposure may be capable of causing these health effects in humans, and these outcomes were not considered for use in deriving toxicity values.

Table ES-1. Health effects with evidence available to synthesize and draw summary judgments and derived toxicity values[a]

Organ/ system	Evidence integration judgment	Toxicity value	Value (mg/kg-d)	Confidence	UF_A	UF_H	UF_S	UF_L	UF_D	UF_C	Basis
Immune (i.e., developmental immune)	**Evidence indicates (likely)**	Lifetime osRfD	**4×10^{-10} (RfD)**	*Medium*	1	10	1	1	3	30	Decreased serum anti-tetanus antibody concentration in children at age 7 yr (Grandjean et al., 2012; Budtz-Jørgensen and Grandjean, 2018)
		Subchronic osRfD	4×10^{-10}	*Medium*	1	10	1	1	3	30	Decreased serum anti-tetanus antibody concentration in children at age 7 yr (Grandjean et al., 2012; Budtz-Jørgensen and Grandjean, 2018)
Thyroid	**Evidence indicates (likely)**	Lifetime osRfD	2×10^{-7}	*Medium*	3	10	1	1	3	100	Decreased serum-total T4 levels in F1 Wistar rat pups at PND 16/17 (Ramhøj et al., 2018)
		Subchronic osRfD	2×10^{-7}	*Medium*	3	10	1	1	3	100	Decreased serum-total T4 levels in F1 Wistar rat pups at PND 16/17 (Ramhøj et al., 2018)

RfD = reference dose (in mg/kg-d) for lifetime exposure; subchronic RfD = reference dose (in mg/kg-d) for less-than-lifetime exposure; osRfD = organ-/system-specific reference dose (in mg/kg-d); UFA = animal to human uncertainty factor; UFC = composite uncertainty factor; UFD = evidence base deficiencies uncertainty factor; UFH = human variation uncertainty factor; UFL = LOAEL to NOAEL uncertainty factor; UFS = subchronic to chronic uncertainty factor.

[a]A summary of pharmacokinetic parameters used for this evaluation is provided in Table 3-6 in Section 3.1.6, Empirical Pharmacokinetic Analysis.

ES.1 LIFETIME AND SUBCHRONIC ORAL REFERENCE DOSE (RfD) FOR NONCANCER EFFECTS

From the identified hazards with sufficient qualitative and quantitative information to support the derivation of candidate lifetime values (i.e., immune and thyroid), decreased serum anti-tetanus antibody concentrations in children (male and female) (Grandjean et al., 2012; Budtz-Jørgensen and Grandjean, 2018) was selected as the basis for the oral RfD of 4×10^{-10} mg/kg-day. A $BMDL_{½SD}$ of 2.82×10^{-4} mg/L in serum was identified for this endpoint and was used as the $POD_{Internal}$. The human equivalent dose POD (POD_{HED}) of 1.16×10^{-8} mg/kg-day was derived by multiplying the $POD_{Internal}$ by the human clearance of 4.1×10^{-5} L/kg-day to estimate human equivalent doses from an internal dose. The overall RfD for PFHxS was calculated by dividing the POD_{HED} by a composite uncertainty factor of 30 to account for interindividual differences in human susceptibility ($UF_H = 10$) and deficiencies in the toxicity evidence base ($UF_D = 3$). The immune organ-/system-specific osRfD is based on the lowest overall POD_{HED} and UF_C; therefore, the selected RfD based on decreased serum anti-tetanus antibody concentration in children (a susceptible lifestage for this effect) is considered protective of the observed health effects associated with lifetime PFHxS exposure. The selection considered both available osRfDs as well as the overall confidence and composite uncertainty for those osRfDs. The thyroid osRfD was based on application of a composite uncertainty threefold greater than that applied in deriving the immune osRfD ($UF_c = 100$ for thyroid versus $UF_c = 30$ for developmental immune effects). Further, when comparing the sensitivity of thyroid and immune osRfDs, the thyroid value is 500-fold higher than the developmental immune endpoint. Selection of the RfD on the basis of developmental immune effects is presumed to be protective of possible thyroid and other potential adverse health effects (including potential effects on birth weight and adverse hepatic effects) in humans. Finally, because the developmental immune osRfD is based on effects observed in males and females, the overall RfD would be protective for both sexes. The same study (Grandjean et al., 2012; Budtz-Jørgensen and Grandjean, 2018) endpoint (decreased serum anti-tetanus antibody concentration in children) and value were selected as the basis for the subchronic RfD of 4×10^{-10} mg/kg-day.

ES.2 CONFIDENCE IN THE ORAL REFERENCE DOSE (RfD) AND SUBCHRONIC RfD

The overall confidence in the RfD and subchronic RfD is *medium* and is driven by *medium* confidence in the overall evidence base for immune effects, *medium* confidence in the (Grandjean et al., 2012; Budtz-Jørgensen and Grandjean, 2018) study (HAWC link), and *medium* confidence in quantitation of the POD (see Section 5.2. and Table 5-8).

ES.3 NONCANCER EFFECTS FOLLOWING INHALATION EXPOSURE

No studies that examine toxicity in humans or experimental animals following inhalation exposure are available and no acceptable physiologically based pharmacokinetic (PBPK) models are available to support route-to-route extrapolation; therefore, no RfC was derived.

ES.4 EVIDENCE FOR CARCINOGENICITY

Under EPA's Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005), EPA concluded there is ***inadequate information to assess carcinogenic potential*** for PFHxS by either the oral or inhalation routes of exposure. This conclusion is based on the lack of adequate data to inform the potential carcinogenicity of PFHxS in the database. This precludes the derivation of quantitative estimates for either oral (oral slope factor [OSF]) or inhalation (inhalation unit risk [IUR]) exposure.