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IRIS Toxicological Review of Perfluorohexanoic Acid [PFHxA, CASRN 307-24-4] and Related Salts

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EXECUTIVE SUMMARY

Summary of Occurrence and Health Effects

Perfluorohexanoic acid (PFHxA, CASRN 307-24-4)[1] and its related salts are members of the group per and polyfluoroalkyl substances (PFAS). This assessment applies to PFHxA as well as salts of PFHxA, including ammonium perfluorohexanoate (PFHxA-NH_4, CASRN 21615-47-4), and sodium perfluorohexanoate (PFHxA-NA, CASRN 2923-26-4), and other nonmetal and alkali metal salts of PFHxA that would be expected to fully dissociate in aqueous solutions of pH ranging from 4–9 (e.g., in the human body) and not release other moieties that would cause toxicity independent of PFHxA. Notably, due to the possibility of PFHxA-independent contributions of toxicity, this assessment would not necessarily apply to nonalkali metal salts of PFHxA (e.g., silver perfluorohexanoate; CASRN 336-02-7). The synthesis of evidence and toxicity value derivation presented in this assessment focuses on the free acid of PFHxA and related ammonium and sodium salts given the currently available toxicity data.

Concerns about PFHxA 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 in the environment; they are manmade compounds that have been used widely over the past several decades in industrial applications and consumer products because of their resistance to heat, oil, stains, grease, and water. PFAS in the environment are linked to industrial sites, military fire training areas, wastewater treatment plants, and commercial products (Appendix A, Section 2.1.2)

The Integrated Risk Information System (IRIS) Program is developing a series of five PFAS assessments (i.e., perfluorobutanoic acid [PFBA], perfluorohexanoic acid [PFHxA], perfluorohexane sulfonate [PFHxS], perfluorononanoic acid [PFNA], perfluorodecanoic acid [PFDA], and their associated salts) 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 PFHxA. The protocol also lays out the systematic review and dose-response methods used to conduct this review (see also Section 1.2). The systematic review protocol was released for public comment in November 2019 and was updated based on those public comments. Appendix A links to the updated version of the protocol and summary of revisions.

[1] The CASRN given is for linear PFHxA; the source PFHxA used in toxicity studies was reported to be >93% pure. No explicit statement that only the linear form was used was available from the studies. Therefore, there is the possibility that a minor proportion of the PFHxA 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.

Human epidemiological studies have examined possible associations between PFHxA exposure and health outcomes, such as liver enzymes, thyroid hormones, blood lipids, blood pressure, insulin resistance, body mass index, semen parameters, reproductive hormones, and asthma. The ability to draw conclusions regarding these associations is limited by the overall conduct of the studies (studies were generally *low* confidence); the few studies per health outcome; and, in some studies, the lack of a quantifiable measure of exposure. No studies were identified that evaluated the association between PFHxA exposure and carcinogenicity in humans.

Animal studies of PFHxA exposure exclusively examined the oral exposure route, and therefore, no inhalation assessment was conducted nor was an RfC derived (see Section 5.2.2). The available animal studies of oral PFHxA exposure examined a variety of noncancer and cancer endpoints, including those relevant to hepatic, developmental, renal, hematopoietic, endocrine, reproductive, immune, and nervous system effects.

Overall, the available **evidence indicates** that PFHxA likely causes hepatic, developmental, hematopoietic, and endocrine (see Sections 3.2.1, 3.2.2, 3.2.4, and 3.2.5, respectively) effects in humans given sufficient exposure conditions. Specifically, for hepatic effects, the primary support for this hazard conclusion included evidence of increased relative liver weights and increased incidence of hepatocellular hypertrophy in adult rats. These hepatic findings correlated with changes in clinical chemistry (e.g., serum enzymes, blood proteins) and necrosis. For hematopoietic effects, the primary supporting evidence included decreased red blood cell counts, decreased hematocrit values, and increased reticulocyte counts in adult rats. Developmental effects were identified as a hazard based on evidence of decreased offspring body weight and increased perinatal mortality in exposed rats and mice. A short-term (28-day) study in rats showed a strong dose dependent effect on serum thyroid hormones in males. Selected quantitative data from these identified hazards were used to derive toxicity values (see Table ES-1).

Although some human and animal evidence was also identified for renal, male, and female reproductive, immune, and nervous system effects, the currently available ***evidence is inadequate*** to assess whether PFHxA may cause these health effects in humans (see Sections 3.2.3, 3.2.6, 3.2.7, 3.2.8, and 3.2.9 respectively) and were not used to derive toxicity values.

Table ES-1. Evidence integration judgments and derived toxicity values for PFHxA

Health system	Evidence integration judgment	Toxicity value type	Value for PFHxA (mg/kg-d)	Value for PFHxA-Na[a] (mg/kg-d)	Value for PFHxA-NH_4[a] mg/kg-d)	Confidence in toxicity value[b]	UF_C[c,d,e]	Basis
Hepatic	*Evidence indicates (likely)*	osRfD	4×10^{-4}	4×10^{-4}	4×10^{-4}	*Medium*	300	Increased hepatocellular hypertrophy in adult rats (Loveless et al., 2009)
		Subchronic osRfD	1×10^{-3}	1×10^{-3}	1×10^{-3}	*Medium*	100	Increased hepatocellular hypertrophy in adult rats (Loveless et al., 2009)
Hematopoietic	***Evidence indicates (likely)***	osRfD	5×10^{-3}	6×10^{-3}	5×10^{-3}	*Medium*	100	Decreased red blood cells in adult rats (Klaunig et al., 2015)
		Subchronic osRfD	8×10^{-4}	8×10^{-4}	8×10^{-4}	*Medium-Low*	100	Decreased red blood cells in adult rats (Chengelis et al., 2009b)
Developmental	***Evidence indicates (likely)***	osRfD	5×10^{-4}	5×10^{-4}	5×10^{-4}	*Medium*	100	Decreased F_1 body weight at PND 0 in rats (Loveless et al., 2009)
		Subchronic osRfD	5×10^{-4}	5×10^{-4}	5×10^{-4}	*Medium*	100	Decreased F_1 body weight at PND 0 in rats (Loveless et al., 2009)
Endocrine	***Evidence indicates (likely)***	osRfD	NA	NA	NA	NA	NA	Not derived due to high degree of uncertainty with deriving a lifetime value from a short-term study.
		Subchronic osRfD	1×10^{-3}	1×10^{-3}	1×10^{-3}	*Medium*	300	Decreased Free T4 in adult male rats (NTP, 2018)
RfD[d]			5×10^{-4}	5×10^{-4}	5×10^{-4}	*Medium*	100	Decreased F_1 body weight at PND 0 in rats (Loveless et al., 2009)
Subchronic RfD[e]			5×10^{-4}	5×10^{-4}	5×10^{-4}	*Medium*	100	Decreased F_1 body weight at PND 0 in rats (Loveless et al., 2009)

See Section 5.2.1 for full details on study and dataset selection, modeling approaches (including BMR selection), uncertainty factor application, candidate value selection, and characterization of confidence in the osRfDs and RfDs.

RfD = reference dose (in mg/kg-day) for lifetime exposure; subchronic RfD = reference dose (in mg/kg-d) for less-than-lifetime exposure; osRfD = organ/system specific oral reference dose (in mg/kg-d); UF_C = composite uncertainty factor which is the product of the interspecies uncertainty factor (UF_A), interindividual human variability uncertainty factor (UF_H), subchronic-to-chronic uncertainty factor (UF_S), LOAEL-to-NOAEL uncertainty factor (UF_L), and database uncertainty factor (UF_D); NA = not applicable.

[a]See Tables 5-7 and 5-11 for details on how to calculate candidate values for salts of PFHxA. The osRfDs presented in this table have been rounded to 1 significant digit from the candidate values presented in Tables 5-7 and 5-11.

[b]The overall confidence in the derived toxicity values is synthesized from confidence judgments regarding confidence in the study used to derive the toxicity value, confidence in the evidence base supporting the hazard, and confidence in the quantification of the point of departure; see Table 5-8 for full details regarding the confidence judgments.

[c]See Table 5-6 for an explanation of the uncertainty factors applied to derive the osRfD and subchronic osRfD values.

[d]Developmental and hematopoietic $UF_C = 100$ based on $UF_A = 3$, $UF_H = 10$, $UF_S = 1$, $UF_L = 1$, and $UF_D = 3$; hepatic $UF_C = 300$ based on $UF_A = 3$, $UF_H = 10$, $UF_S = 3$, $UF_L = 1$, and $UF_D = 3$.

[e]Hepatic, developmental, and hematopoietic $UF_C = 100$ based on $UF_A = 3$, $UF_H = 10$, $UF_S = 1$, $UF_L = 1$, and $UF_D = 3$; endocrine $UF_C = 300$ based on $UF_A = 3$, $UF_H = 10$, $UF_S = 3$, $UF_L = 1$, and $UF_D = 3$.

ES.1 CHRONIC ORAL REFERENCE DOSE (RFD) FOR NONCANCER EFFECTS

From the identified hazards of potential concern (i.e., endocrine, hepatic, hematopoietic, and developmental toxicity), decreased offspring body weight in neonatal rats (Loveless et al., 2009) was selected as the basis for the RfD of 5×10^{-4} mg/kg-day. A $BMDL_{5RD}$ of 10.62 mg/kg-day was identified for this endpoint and was used as the point of departure (POD). The human equivalent dose POD (POD_{HED}) of 0.048 mg/kg-day was derived by applying the ratio of the clearance between female rats and humans and a normalization from the sodium salt to the free acid using a molecular weight conversion. The overall RfD for PFHxA was calculated by dividing the POD_{HED} by a composite uncertainty factor of 100 to account for pharmacodynamic uncertainty in the extrapolation from rats to humans (UF_A = 3), interindividual differences in human susceptibility (UF_H = 10), and deficiencies in the toxicity evidence base (UF_D = 3).

ES.2 CONFIDENCE IN THE ORAL REFERENCE DOSE (RFD)

The study conducted by Loveless et al. (2009) reported developmental effects following administration of PFHxA sodium salt to pregnant Sprague-Dawley rats dosed by gavage for approximately 70 days prior to cohabitation through gestation and lactation, for a total of 126 days daily gavage with 0, 20, 100, or 500 mg/kg-day sodium PFHxA. The overall confidence in the osRfD is medium and is primarily driven by medium confidence in the overall evidence base for developmental effects, high confidence in the study (click the HAWC link for full study evaluation details), and medium confidence in quantitation of the POD (see Table 5-8). High confidence in the study was not interpreted to warrant changing the overall confidence in the RfD from medium.

ES.3 SUBCHRONIC ORAL REFERENCE DOSE (RFD) FOR NONCANCER EFFECTS

In addition to providing RfDs for chronic oral exposures in multiple systems, a less-than-lifetime subchronic RfD was derived for PFHxA. The same study and endpoint (Loveless et al., 2009) and decreased F_1 body weight and value was selected as the basis for the subchronic RfD of 5×10^{-4} mg/kg-day (see Table ES-1). Details are provided in Section 5.2.1.

ES.4 NONCANCER EFFECTS FOLLOWING INHALATION EXPOSURE

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

ES.5 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 PFHxA by all routes of exposure. The lack of data on the carcinogenicity of PFHxA precludes the derivation of quantitative estimates for either oral (oral slope factor [OSF]) or inhalation (inhalation unit risk [IUR]) exposure (see Section 3.3