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IRIS Toxicological Review of Perfluorobutanoic Acid (PFBA, CASRN 375-22-4) and Related Salts

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EXECUTIVE SUMMARY

Summary of Occurrence and Health Effects

Perfluorobutanoic acid (PFBA, CASRN 375-22-4)[1] and its related salts are members of the group of per- and polyfluoroalkyl substances (PFAS). This assessment applies to PFBA as well as salts (including alkali metal salts) of PFBA that would be expected to fully dissociate in aqueous solutions of pH ranging from 4–9 (e.g., in the human body). Thus, while this assessment would not necessarily apply to non-alkali metal salts of PFBA (e.g., silver heptafluorobutyrate; CASRN 3794-64-7) due to the possibility of PFBA-independent contributions of toxicity, it does apply to PFBA salts including ammonium perfluorobutanoate (CASRN 10495-86-0), sodium perfluorobutanoate (CASRN 2218-54-4), potassium heptafluorobutanoate [2966-54-3], and other non-metal or alkali metal salts of PFBA. The synthesis of evidence and toxicity value derivation presented in this assessment focuses on the free acid of PFBA and ammonium perfluorobutanoate given the currently available toxicity data.

Concerns about PFBA 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 consumer products and industrial applications because of their resistance to heat, oil, stains, grease, and water. PFBA is a breakdown product of other PFAS that are used in stain-resistant fabrics, paper food packaging, and carpets; it was also used for manufacturing photographic film, and it is used as a substitute for longer chain perfluoroalkyl carboxylic acids (PFCAs) in consumer products. PFBA has been found to accumulate in agricultural crops and has been detected in household dust, soils, food products, and surface, ground, and drinking water. As such, exposure is possible via inhalation of indoor or outdoor air, ingestion of drinking water and food, and dermal contact with PFBA-containing products.

Human epidemiological studies have examined possible associations between PFBA exposure and health outcomes, such as thyroid hormones or disease, hepatic enzymes, birth outcomes (e.g., birth weight, gestational duration), semen parameters, blood lipids, and blood pressure. The ability to draw conclusions regarding these associations is limited due to the methodological conduct of the studies (studies were generally considered *low* confidence for these outcomes; two studies on congenital hypothyroidism and birth weight and gestational duration

[1] The CASRN given is for linear PFBA; the source PFBA used in toxicity studies was reported to be 98% pure (Das et al., 2008)and reagent grade (Butenhoff et al., 2012a). Neither study explicitly states that only the linear form was used. Therefore, there is the possibility that a minor proportion of the PFBA 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.

were considered *uninformative*); the small number of studies per health outcome; and the generally null findings coincident with notable sources of study insensitivity due to lack of detecting quantifiable levels of PFBA in blood samples or a narrow concentration range across exposure groups. No studies were identified that evaluated the association between PFBA exposure and carcinogenicity.

Animal studies of PFBA exposure in rats and mice have exclusively examined the oral route (i.e., no inhalation or dermal studies were identified during the literature search) and have examined noncancer endpoints only.

Altogether, the available ***evidence indicates*** that developmental, thyroid, and liver effects in humans are likely caused by PFBA exposure in utero or during adulthood (see Sections 3.2.1, 3.2.2, and 3.2.3). There was ***inadequate evidence*** to determine whether reproductive effects might represent a potential human health hazard following PFBA exposure (see Section 3.2.4).

The few epidemiological studies did not inform the potential for effects in the thyroid, liver, reproductive system, or developing offspring, and the evidence integration judgments are based on PFBA studies in animals. Liver effects manifested as increased relative liver weight in adult animals and increased incidence of hepatocellular hypertrophy (see Section 3.2.2 and Tables 3-6 and 3-7). Thyroid effects in adult exposed rats were expressed through decreases in free and total thyroxine (T4) and increased incidence of thyroid follicular hypertrophy and hyperplasia (see Section 3.2.1 and Tables 3-3 and 3-2). Developmental effects in exposed animals were expressed as the loss of viable offspring (total litter resorption), and postnatal delays in postnatal developmental milestones: eye opening, vaginal opening, and preputial separation (see Section 3.2.3 and Table 3-9).

Table ES-1 summarizes the evidence integration judgments for health effects that had enough evidence available to synthesize and draw hazard conclusions, and the toxicity values derived for those health effects.

Table ES-1. Evidence integration judgements and derived toxicity values for PFBA

Health system	Evidence integration judgment	Toxicity value type	Value PFBA (mg/kg-d)	Value NH_4^+ PFB (mg/kg-d)[a]	Confidence in Toxicity Value[b]	UF_C[c]	Basis
Hepatic	*Evidence indicates (likely)*	osRfD	1×10^{-3}	1×10^{-3}	*Medium*	1,000[d]	Increased hepatocellular hypertrophy in adult rats
		Subchronic osRfD	1×10^{-2}	1×10^{-2}	*Medium*	100[e]	Increased hepatocellular hypertrophy in adult rats

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Thyroid	*Evidence indicates (likely)*	osRfD	1×10^{-3}	1×10^{-3}	*Medium-low*	1,000[d]	Decreased total T4 in adult rats
		Subchronic osRfD	1×10^{-2}	1×10^{-2}	*Medium-low*	100[e]	Decreased total T4 in adult rats
Developmental	*Evidence indicates (likely)*	osRfD	6×10^{-3}	7×10^{-3}	*Medium-low*	100[e]	Developmental delays in mice[f]
		Subchronic osRfD	6×10^{-3}	7×10^{-3}	*Medium-low*	100[e]	Developmental delays in mice[f]
Reproductive	*Evidence inadequate*	osRfD	Not derived	Not derived	NA	NA	NA
		Subchronic osRfD	Not derived	Not derived	NA	NA	NA
RfD			1×10^{-3}	1×10^{-3}	*Medium*	1,000[d]	Hepatic and thyroid effects
Subchronic RfD			6×10^{-3}	7×10^{-3}	*Medium-low*	100[e]	Developmental effects[f]

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-specific oral reference dose (in mg/kg-d); UF_C = composite uncertainty factor; NA = not applicable.

[a] See Tables 5-7 and 5-10 for details on how to calculate candidate values for salts of PFBA. The osRfDs presented in this table have been rounded to 1 significant digit from the candidate values presented in Tables 5-7 and 5-10.

[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 for these confidence judgments.

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

[d] UF_C = 1,000 comprised of UF_A = 3, UF_H = 10, UF_S = 10, UF_L = 1, and UF_D = 3.

[e] UF_C = 100 comprised of UF_A = 3, UF_H = 10, UF_S = 1, UF_L = 1, and UF_D = 10.

[f] The point of departure represents three types of developmental delays observed in the same study.

Chronic Oral Reference Dose (RfD) for Noncancer Effects

From the identified human health hazards of potential concern (liver, thyroid, developmental toxicity), increased liver hypertrophy and decreased T4 in adult male rats after subchronic exposure, as reported in Butenhoff et al. (2012a), were selected as the basis for the oral reference dose (RfD) (see Section 5.2.1). A no-observed-adverse-effect level (NOAEL) of 6 mg/kg-day NH_4^+PFB was identified for increased liver hypertrophy, and a NOAEL of 6 mg/kg-day NH_4^+PFB was identified for decreased T4 (see Table 5-4). These values were used as the points of departure (PODs). After converting the PODs from units of mg/kg-day NH_4^+PFB to units of mg/kg-day PFBA

(by multiplying by the ratio of the molecular weights of the free acid and the ammonium salt), the ratio of serum clearance values between rats and humans was used to account for pharmacokinetic differences between species (see Table 5-3), resulting in the human equivalent doses (POD_{HED}) of 1.15 mg/kg-day and 1.27 mg/kg-day for increased liver hypertrophy and decreased T4, respectively. The RfD for PFBA was calculated by dividing the POD_{HED} values by a composite uncertainty factor (UF_C) of 1,000 to account for residual pharmacokinetic and pharmacodynamic uncertainty in the extrapolation from rats to humans (UF_A = 3), interindividual differences in human susceptibility (UF_H = 10), extrapolation from a subchronic-to-chronic exposure duration (UF_S = 10), and deficiencies in the toxicity database (UF_D = 3) (see Table 5-5). The selected overall RfD for PFBA derived based on liver and thyroid effects is 1×10^{-3} mg/kg-day.[2],[3]

Confidence in the Oral Reference Dose (RfD)

The overall confidence in the RfD is *medium*, based on the confidence in the principal study, confidence in the quantification of the PODs, and confidence in the evidence bases supporting the thyroid and liver effects (see Table 5-8). The subchronic exposure toxicity study conducted by Butenhoff et al. (2012a) reported on administration of NH_4^+PFB by gavage to Sprague-Dawley (S-D) rats for 90 days. This study is rated as *high* confidence with adequate reporting and appropriate study design, methods, and conduct (see study evaluation analysis in Health Assessment Workspace Collaborative [HAWC]).[4] Confidence in the oral toxicity database for derivation of the RfD is *medium* because consistent and coherent effects occurred within both individual organ systems used to support the RfD, although important uncertainties remain. Confidence in the quantification of the PODs supporting the RfD is *medium*, given (1) use of a NOAEL roughly equivalent to BMDL (suggesting that this POD might not be more substantially more uncertain than a BMD-based POD); (2) use of a NOAEL roughly equivalent with a decrease of one standard deviation for thyroid effects (demonstrating that the NOAEL would be roughly equivalent to the BMD, but higher than the BMDL, if BMD modeling had been conducted); and (3) dosimetric adjustments using PFBA-specific pharmacokinetic information (see Table 5-8).

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[2] See Table 5-7 for details on how to calculate candidate values for salts of PFBA; briefly, the candidate values for different salts of PFBA would be calculated by multiplying the candidate value for the free acid of PFBA by the ratio of molecular weights. For example, for the ammonium salt the ratio would be: $\frac{MW\ ammonium\ salt}{MW\ free\ acid} = \frac{231}{214} = 1.079$. This same method of conversion can be applied to other salts of PFBA, such as the potassium or sodium salts, using the corresponding molecular weights.

[3] Note that the RfD for the free acid presented in this document and an RfD for the anion of PFBA (perfluorobutanoate, $C_3F_7CO_2^-$, CASRN 45048-62-2) would be practically identical given the molecular weights between the two compounds differ by less than 0.5%, (i.e., by the weight of a single hydrogen atom).

[4] HAWC is a modular content management system designed to store, display, and synthesize multiple data sources for the purpose of producing human health assessments of chemicals. This online application documents the overall workflow of developing an assessment from literature search and systematic review to data extraction (human epidemiology, animal bioassay, and in vitro assay), dose-response analysis, and finally evidence synthesis and visualization. In order to view HAWC study evaluation results, visualizations, etc., users must create first create a free account; see https://hawcprd.epa.gov/about for more details.

Noncancer Effects Observed Following Inhalation Exposure

No studies are available that examine toxicity in humans or experimental animals following inhalation exposure, and no physiologically based pharmacokinetic (PBPK) models exist to allow a route-to-route extrapolation; therefore, no inhalation reference concentration (RfC) was derived (see Section 5.2.3).

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 PFBA by either oral or inhalation routes of exposure (see Section 3.2.5). This conclusion precludes the derivation of quantitative estimates for either oral (oral slope factor [OSF]) or inhalation (inhalation unit risk [IUR]) exposure (see Section 5.3).

Subchronic Oral Reference Dose (RfD) for Noncancer Effects

In addition to providing organ/system-specific RfDs for lifetime exposures in multiple systems, less-than-lifetime (subchronic) RfDs also were derived (see Section 5.2.2 and Tables 5-9 and 5-10). In the case of PFBA, all studies used to calculate the subchronic values were subchronic or gestational in duration. Therefore, the method to calculate the organ/system-specific subchronic RfDs is identical to that used for calculating the organ/system-specific RfDs, except in the application of the UF_S (e.g., the use of a UF_S = 1 rather than 10 for subchronic studies given there is no extrapolation to a chronic exposure duration). Thus, the individual organs and systems for which specific subchronic RfD values were derived were the liver, thyroid, and developing fetus. The value for the developing fetus was selected for the subchronic RfD. A BMDL of 3.8 mg/kg-day NH_4^+PFB for increased time to vaginal opening in neonatal female mice was used as the basis for the POD. After converting the PODs from units of mg/kg-day NH_4^+PFB to units of mg/kg-day PFBA (by multiplying by the ratio of the molecular weights of the free acid and the ammonium salt), the HED was calculated by multiplying the POD for the free acid by the ratio of serum clearance values between mice and humans. The subchronic RfD for PFBA was calculated by dividing the POD_{HED} of 0.62 mg/kg-day PFBA by a composite uncertainty factor of 100 to account for extrapolation from rats to humans (UF_A = 3), for interindividual differences in human susceptibility (UF_H = 10), and deficiencies in the toxicity database (UF_D = 3). The subchronic RfD derived from the effects on delayed time to vaginal opening, as representative of general developmental delays, was 6×10^{-3} mg/kg-day[5].

[5] See Table 5-10 for details on how to calculate subchronic candidate values for salts of PFBA; briefly, the candidate values for different salts of PFBA would be calculated by multiplying the candidate value for the free acid of PFBA by the ratio of molecular weights. For example, for the ammonium salt the ratio would be: $\frac{MW\ ammonium\ salt}{MW\ free\ acid} = \frac{231}{214} = 1.079$. This same method of conversion can be applied to other salts of PFBA, such as the potassium or sodium salts, using the corresponding molecular weights.