Technical Fact Sheet: Toxicity Assessment for PFBS

EPA finalized and released the toxicity assessment for perfluorobutane sulfonic acid (PFBS) and its potassium salt, potassium perfluorobutane sulfonate (K+PFBS) based on the Agency's analysis of the best available science on the health effects of these chemicals. The toxicity information and values included in this assessment can be used by EPA and other federal agencies, and state, tribal, and local communities, along with specific exposure and other relevant information, to determine, under appropriate statutes, if and when it is necessary to take action to address potential risk associated with human exposure to PFBS.

Background on PFBS

PFBS is a four-carbon PFAS that was developed as a replacement for perfluorooctane sulfonic acid (PFOS), a chemical that was voluntarily phased out by the primary U.S. manufacturer by 2002. PFBS has been identified in the environment and consumer products, including surface water, wastewater, drinking water, dust, carpeting and carpet cleaners, and floor wax. PFBS is persistent in the environment and mobile in groundwater and surface water.

EPA's PFBS Toxicity Assessment

In the human health risk assessment paradigm, a toxicity assessment covers the first two steps (Step 1. Hazard Identification and Step 2. Dose-Response) of the four-step process, described by the National Academy of Science in 1983 as "the characterization of the potential adverse health effects of human exposures to environmental hazards." Characterizing risk, which is not done in these toxicity assessments, would require additional consideration of exposure. For further details about risk assessment see: https://www.epa.gov/risk/conducting-human-health-risk-assessment.

EPA's toxicity assessment for PFBS includes the first two steps of the human health risk assessment paradigm described above, including developing chronic and subchronic oral reference doses (RfDs). A RfD is a toxicity value specifically for non-cancer effects associated with the oral (ingested) route of exposure. A RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. For PFBS, the subchronic RfD is based on the same hazard and dose-response information as the chronic RfD but is specifically derived for less-than-lifetime exposure scenarios. RfDs can be derived from a no-observed-adverse-effect level (NOAEL), lowest-observed-adverse-effect level (LOAEL), or benchmark dose (through quantitative modeling), with

uncertainty factors applied to reflect limitations of or gaps in the data available. The higher the RfD, the higher the chemical dose needed to elicit potential adverse health effects.

EPA followed the general guidelines for risk assessment set by the National Research Council (1983) and characterized in a variety of EPA risk assessment guidance and recommendations[1] in identifying the health hazards and determining the points of departure (PODs) considered for the derivation of the RfDs for PFBS. Consistent with the recommendations presented in EPA Guidelines, EPA considered and applied uncertainty factors to the selected PODs to address, where applicable, intraspecies variability, interspecies variability, deficiencies in the database, extrapolating from LOAELs to NOAELs, and extrapolation of study data from a subchronic to a chronic exposure duration to develop the toxicity values.

The PFBS toxicity assessment underwent multiple rounds of agency, interagency, and independent, external, expert peer review as well as public review and comment. EPA considered the reviewers' comments at each stage and revised the draft assessment accordingly. External peer review comments and EPA's responses can be viewed at: https://www.epa.gov/pfas/learn-about-human-health-toxicity-assessment-pfbs. The public comments are available on Regulations.gov in the Docket ID No. EPA-HQ-OW-2018-0614.

PFBS: Health Effects Summary

High and medium confidence animal (rat and mouse) toxicity studies from oral exposure to PFBS and its potassium salt were available for acute, short-term, subchronic, and gestational exposure durations, as well as a two-generation reproductive toxicity study. A group of low and medium confidence human studies of PFBS exposure and health effects were identified, but their ability to inform conclusions was limited. Health outcomes evaluated across available studies included effects on the thyroid, reproductive organs and tissues, development, liver, lipids and lipoproteins, and kidneys following oral exposure to PFBS. Based on information across different sexes, lifestages, and durations of exposure, the thyroid appears to be particularly sensitive to oral PFBS exposure.

PFBS: Reference Doses

Subchronic and chronic RfDs were derived for thyroid effects associated with PFBS. The principal study chosen for determining the subchronic and chronic RfDs for PFBS and its potassium salt is the oral gestational exposure study in mice (Feng et al., 2017) and the critical effect is on the thyroid (decreased serum total thyroxine, T4) in neonatal offspring. Using EPA's Benchmark Dose Technical Guidance Document (2012), benchmark dose modeling was used to empirically model the dose-response relationship in the range of observed data. Additionally, toxicokinetic data exists for PFBS in relevant animal species (i.e., rats and mice) and humans, such that a data-informed adjustment approach for estimating the dosimetric adjustment factor (DAF) can be used. Specifically, in *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (USEPA, 2011), the EPA endorses

[1] www.epa.gov/risk/risk-assessment-guidelines#tab-1

a hierarchy of approaches to derive human equivalent oral exposures from data from laboratory animal species, with the preferred approach being physiologically based toxicokinetic (PBTK) modeling. In the absence of a PBTK model for PFBS, chemical-specific information informed derivation of human equivalent oral exposures. The EPA concluded that data for PFBS are adequate to support derivation of a data-informed dosimetric adjustment. The resulting point of departure (POD) human equivalent dose (HED) for decreased T4 in neonatal offspring is 0.095 mg/kg-day. Uncertainty factors applied include a 10 for intraspecies variability (UF_H), 3 for interspecies differences (UF_A), 1 because the POD is a BMDL (UF_L), 1 for duration extrapolation because the POD comes from a developmental study (UF_S), and 3 for database deficiencies (UF_D), including the lack of developmental neurotoxicity and immune effect studies, to yield a subchronic RfD of 0.001 mg/kg-day (Table 1). In the derivation of the chronic RfD, in addition to the uncertainty factors above, the UF_D was increased to 10 to further account for the lack of chronic duration studies, to yield a chronic RfD of 0.0003 mg/kg-day (Table 1).

Table 1. Summary of Reference Doses for PFBS

	Principal Study	Critical Effect	POD (HED)*	Total UF	RfD
Subchronic RfD	Gestational exposure study (GD1-20); Feng et al. (2017)	Decreased serum total T4 in newborn (PND1) mice	$BMDL_{0.5SD}$ = 0.095 mg/kg-day	UF_H-10 UF_A-3 UF_L-1 UF_S-1 UF_D-3 Total UF-100	**0.001 mg/kg-day**
Chronic RfD	Gestational exposure study (GD1-20); Feng et al. (2017)	Decreased serum total T4 in newborn (PND1) mice	$BMDL_{0.5SD}$ = 0.095 mg/kg-day	UF_H-10 UF_A-3 UF_L-1 UF_S-1 UF_D-10 Total UF-300	**0.0003 mg/kg-day**

** The Human Equivalent POD (POD [HED]) was calculated from the mouse POD using a data-informed dosimetric adjustment factor based on PFBS-specific toxicokinetic data for mice (Lau et al., 2020) and humans (Xu et al., 2020) as per EPA guidance (US EPA, 2011)*

Chronic Toxicity Comparison

EPA previously published health effects support documents for two other PFAS: PFOA and PFOS. Based on these EPA assessments, the chronic RfD for PFBS is approximately more than an order of magnitude (~15x) higher than the chronic RfDs for these other PFAS (Table 2). Based on currently available animal toxicity data, it appears that PFBS is less toxic than PFOA and PFOS.

Table 2. Comparison of Chronic Toxicity for PFAS With EPA Health Effects Assessments

Chemical [Citation]	**EPA Chronic RfD [mg/kg-day]**	**Critical Effect (Study)**
PFBS [EPA 2021 (FINAL)]	0.0003	Decreased serum T4 in newborn mice (Feng et al., 2017)
PFOA [EPA 2016a (FINAL)]	0.00002	Skeletal effects and accelerated puberty in males (Lau et al., 2006)
PFOS [EPA 2016b (FINAL)]	0.00002	Decreased pup weight in rats (Luebker et al., 2005)

Applications for Risk Assessment and Risk Management

The PFBS toxicity assessment is one of the key goals of the Agency's PFAS Action Plan and provides qualitative and quantitative toxicity information that can be used along with exposure information and other important considerations to assess potential health risks to determine if, and when, it is appropriate to take action to address this chemical. This assessment is available for use across multiple EPA program and regional offices, other federal agencies, states, tribes, external stakeholders, and other entities as needed. One use of this assessment is to update and replace the existing 2014 Provisional Peer Reviewed Toxicity Value (PPRTV) for PFBS assessment used by the EPA's Superfund Program.

The RfDs and associated hazard evidence in the toxicity assessment for PFBS provides information on health effects and can be combined with specific exposure information to inform health-based national standards, clean-up levels at local sites, and non-regulatory advisory levels. RfDs can be applied in a variety of exposure scenarios to help characterize potential risk from chemical exposure. RfDs can alsobe used to develop health protective levels for chemicals in water, soil, and other media through further analyses. For example, RfDs can be combined with exposure information in risk assessments, and subsequent risk management activities can lead to development of regulatory standards (e.g., Maximum Contaminant Levels) or non-regulatory guideline values (e.g., health advisories) for drinking water under the Safe Drinking Water Act (SDWA), and human health water quality criteria for permitting discharges into ambient waters under the Clean Water Act (CWA). RfDs are also used in risk assessments under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA), also known as Superfund; under the CWA for pollutants in biosolids; and under the Resource Conservation and Recovery Act (RCRA) to develop cleanup levels for contaminated soil and groundwater. The levels developed for these risk management tools may vary due to the type of exposure being evaluated. As

such, the RfD is not meant to be the standard itself, but an early piece of the risk assessment along with other information considered by risk managers to develop those standards.

The EPA will work with our state, tribal, and local partners to provide technical assistance as they consider the PFBS RfDs in relevant exposure scenarios. Under the risk assessment/risk management paradigm the supporting science, as well as statutory and legal considerations, risk management options, potential public health impacts, cost/benefit analyses, economic and social factors, and other considerations are weighed and integrated. All users are advised to review the information provided in this document to ensure that the assessment is appropriate for the types of exposures and circumstances in question and the risk management decisions that would be supported by the risk assessment.

How to Learn More

To view the toxicity assessment and other related information on PFBS, visit https://www.epa.gov/pfas/learn-about-human-health-toxicity-assessment-pfbs.

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