Per- and Polyfluoroalkyl Substances (PFAS): Next Steps for Screening-Level Hazard, Exposure, and Risk Assessment

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Table of Contents

Tables

Figures

Acronyms and Abbreviations

Acronym/Abbreviation	Term/Definition
6:2 FTOH	6:2 fluorotelomer alcohol
8:2 FTOH	8:2 fluorotelomer alcohol
ADI	acceptable daily intake
AGD	anogenital distance
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate aminotransferase
ANSES	French Agency for Food, Environmental and Occupational Health and Safety
APFO	ammonium perfluorooctanoate
ATSDR	Agency for Toxic Substances and Disease Registry
BMC	benchmark concentration
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
CADD	chronic average daily dose
CASRN	Chemical Abstracts Service Registry Number
CDF	cumulative distribution function
CEC	Commission for Environmental Cooperation
CPSC	Consumer Product Safety Commission
DFE	1,1-difluoroethane
DNEL	derived-no-effect-level
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EPA	U.S. Environmental Protection Agency
FTCA	fluorotelomer carboxylic acid
FTOH	fluorotelomer alcohol
GD	gestation day
GM	geometric mean
HCT	hematocrit
HED	human equivalent dose
HGB	hemoglobin
HQ	hazard quotient
IARC	International Agency for Research on Cancer
ICE	Integrated Chemical Environment
IRIS	Integrated Risk Information System

Acronym/Abbreviation	Term/Definition
iTV	indicative toxicity value
JRC	Joint Research Centre
LD	lactation day
LOAEL	lowest-observed-adverse-effect level
LOD	limit of detection
LOQ	limit of quantification
MOA	mode of action
MRL	minimal risk level
NA	not applicable
NHANES	National Health and Nutrition Examination Survey
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
OEHHA	Office of Environmental Health and Hazard Assessment
P5	5th percentile
P95	95th percentile
PECO	populations, exposures, comparators, and outcomes
PFAA	perfluoroalkyl acid
PFAS	per- and polyfluoroalkyl substance
PFBA	perfluorobutanoic acid
PFBS	perfluorobutanesulfonic acid
PFCA	perfluoroalkyl carboxylic acids
PFHpA	perfluoroheptanoic acid
PFHxA	perfluorohexanoic acid
PFHxS	perfluorohexanesulfonic acid
PFNA	perfluorononanoic acid
PFOA	perfluorooctanoic acid
PFOS	perfluorooctane sulfonic acid
PFOSA	perfluorooctanesulfonamide
PFSA	perfluoroalkyl sulfonic acids
POD	point of departure
PPARα	peroxisome proliferator–activated receptor-alpha
PPRTV	Provisional Peer-Reviewed Toxicity Values
Pr	cumulative probability
PUC	product use category
RAX	read-across
RBC	red blood cell

Acronym/Abbreviation	Term/Definition
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RfC	reference concentration
RfD	reference dose
RIVM	Dutch National Institute for Public Health and the Environment
RPF	relative potency factor
SEM	systematic evidence map
SHEDS-HT	Stochastic Human Exposure and Dose Simulation High-Throughput
T3	triiodothyronine
T4	thyroxine
TC	total cholesterol
TCEQ	Texas Commission on Environmental Quality
TDI	tolerable daily intake
TFE	1,1,1,2-tetrafluoroethane
TRV	toxicity reference value
TSH	thyroid stimulating hormone
TWI	tolerable weekly intake
UBA	German Environmental Agency, Umwelt Bundesamt
UF	uncertainty factor
UFA	uncertainty factor for interspecies variability
UFH	uncertainty factor for intraspecies variability
UFL	uncertainty factor if a LOAEL was used in place of a NOAEL
UFS	uncertainty factor for subchronic to chronic extrapolation

1. Introduction

Per- and polyfluoroalkyl substances (PFAS) are known for their stain-resistance, nonstick, and waterproofing properties and have been used in various consumer, commercial, and industrial products. Certain PFAS chemicals have also been associated with a variety of different health effects in several organ systems. There is a need to better understand the potential human health risks associated with PFAS exposures due to their widespread use and persistence in the environment. The perfluoroalkyl acids (PFAAs) class, including chemicals with fully fluorinated aliphatic carbon chains, are the most frequently studied for human health toxicity. The strength of the carbon-fluorine bond makes PFAAs very stable in the environment and leads to their bioaccumulation in humans and other organisms. PFAAs include perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS), which have been phased out of production in many countries, although they are still commonly detected in human populations around the world. One possible contributing source of this continued exposure is the manufacture and use of consumer products containing precursor chemical substances, which can degrade or biotransform into terminal PFAAs in the environment and in the human body (Sunderland et al., 2019; EFSA, 2020; ATSDR, 2021). For example, precursors such as fluorotelomer alcohols (FTOHs) and perfluoroalkyl sulfonamides can form terminal PFAAs in the environment via abiotic and biotic processes (ATSDR, 2021). Additionally, fluorotelomer alcohols have been shown to metabolize into terminal perfluoroalkyl carboxylic acids in humans and experimental animals when inhaled or orally ingested (Nilsson et al., 2013; Rice et al., 2020).

This report presents the findings from a screening-level human health risk assessment conducted on a subset of PFAS chemicals and builds on previous CPSC efforts described in the white paper *Characterizing PFAS Chemistries, Sources, Uses, and Regulatory Trends in U.S. and International Markets* (RTI, 2023). The basic steps for a screening-level risk assessment are (i) hazard identification, (ii) dose-response assessment, (iii) exposure assessment, and (iv) risk characterization. For the purposes of this report, hazard identification and dose-response assessment are discussed together under "hazard assessment." Our objectives were to determine the initial hazards, exposures, and human health risks of 10 targeted PFAS chemicals with the aim to further the understanding of potential PFAS-containing consumer products, possible exposure pathways, and associated chronic human health hazards and risks.

For hazard assessment, toxicity reference values (TRVs) quantify the potency of a substance or estimates dose levels to which people can be exposed for a specified duration of time without an adverse effect. Examples of TRVs include reference doses (RfD), reference concentrations (RfC), acceptable daily intakes (ADI), minimal risk levels

(MRL), and cancer potency estimates (e.g., oral cancer slope factors, inhalation unit risks). This report identified existing TRVs from authoritative sources (i.e., published agency assessments) for the subset of targeted PFAS chemicals. When no existing agency TRV existed, candidate TRVs were developed from (i) nonauthoritative risk assessments/studies, (ii) benchmark dose (BMD) modeling using data from studies identified during hazard identification that could be used for a point of departure (POD) calculation, and/or (iii) read-across extrapolations from chemicals similar to the targeted PFAS. From the candidate TRVs derived using these approaches, a single TRV was selected and carried forward through the risk assessment process.

For exposure assessment, the magnitude, frequency, and duration of exposure to an agent (e.g., chemical substance) is estimated or measured and the exposed population is described. For the subset of targeted PFAS chemicals, published doses by exposure pathway (e.g., diet) from authoritative sources were first identified. When published doses were not available, exposures were estimated using (i) mechanistic models, (ii) empirical measurements, and/or (iii) a reverse dosimetry approach with biomonitoring data. Doses from the three different approaches were provided for the general population by age group and by pathway when relevant.

For risk characterization, information from the hazard and exposure assessments were integrated to synthesize an overall screening-level conclusion about risk. For the targeted PFAS chemicals, this report derives risk values in the form of a hazard quotient (HQ), which is a quantitative estimate of risk. Uncertainties concerning the breadth and depth of toxicity data available for targeted chemicals, particularly regarding issues of hazard identification and TRV derivation, necessitated that we use a probabilistic approach to characterize risk. This approach allowed for incorporation of the uncertainty, particularly in the TRV estimate.

In addition to presenting the hazard, exposure, and risk estimates for a subset of targeted PFAS chemicals, this report documents the factors affecting the uncertainty in each estimate. Specific data needs that could help reduce uncertainty and refine estimates are also identified and discussed.

2. Scope of Work

As part of work conducted under this call order (Call Order No. 61320623F2025), individual PFAS and consumer product combinations were previously categorized and ranked to identify a prioritized subset of chemicals for screening-level risk assessment. Of more than 16,000 PFAS chemicals, 326 were initially identified to have (i) toxicity data and (ii) known or potential uses in consumer products. Chemicals were then qualitatively ranked depending on exposure potential and data availability (see Supplemental File A

for details). From the final set of 35 prioritized chemicals determined to have sufficient information to assess initial hazards, exposures, and risks, the 10 chemicals listed in Table 1 were selected by CPSC staff for evaluation in this report.

Table 1. List of PFAS Chemicals for Evaluation.

CASRN	Chemical Name	Chemical Abbreviation	PFAS Category	Chain Length
647-42-7	6:2 Fluorotelomer alcohol	6:2 FTOH	Fluorotelomer alcohols	6
678-39-7	8:2 Fluorotelomer alcohol	8:2 FTOH	Fluorotelomer alcohols	8
754-91-6	Perfluorooctanesulfonamide	PFOSA	Perfluoroalkane sulfonamides	8
375-22-4	Perfluorobutanoic acid	PFBA	Perfluorocarboxylic acids	4
375-85-9	Perfluoroheptanoic acid	PFHpA	Perfluorocarboxylic acids	7
307-24-4	Perfluorohexanoic acid	PFHxA	Perfluorocarboxylic acids	6
375-73-5	Perfluorobutanesulfonic acid	PFBS	Perfluorosulfonic acids	4
75-37-6	1,1-Difluoroethane	DFE	Short-chain hydrofluorocarbons	2
811-97-2	1,1,1,2-Tetrafluoroethane	TFE	Short-chain hydrofluorocarbons	2
3825-26-1	Ammonium perfluorooctanoate	APFO	Perfluoroalkyl carboxylate salt	8

While ammonium perfluorooctanoate (APFO) was initially identified as a targeted PFAS chemical for our screening-level risk assessment, we were unable to conduct an exposure assessment because we could not identify specific consumer products with APFO. As such, this report focuses on the hazards, exposures, and risks of the remaining nine PFAS chemicals, with a brief discussion of APFO in Section 4.4.

In addition, this report presents the hazards and risks associated with chronic exposure to the targeted chemicals. Acute exposures associated with huffing[1] and corresponding acute hazards and risks for 1,1-difluoroethane (DFE) and 1,1,1,2-tetrafluoroethane (TFE) are discussed in Supplemental File B.

3. Methods

3.1. Literature Search and Screening

3.1.1. Gray Literature Search

We compiled existing TRVs and PODs for the targeted PFAS chemicals by searching the websites of authoritative governmental and nongovernmental health agencies. Each PFAS

[1] Huffing is the term typically used to describe the practice of inhaling chemical fumes from common household products to achieve a brief euphoric high.

was searched by chemical name, common synonyms, common abbreviations, and CASRN. The following websites were searched for all targeted PFAS chemicals:

- Agency for Toxic Substances and Disease Registry – Toxicological Profiles
- U.S. EPA Office of Research and Development, Integrated Risk Information System – Chemical Assessment Summaries and Toxicological Reviews
- U.S. EPA Superfund Program – Provisional Peer-Reviewed Toxicity Values
- U.S. EPA Office of Pollution Prevention and Toxics – Final Risk Evaluations
- U.S. EPA Other Assessments (e.g., Human Health Toxicity Assessments; Drinking Water Health Advisories)
- California Office of Environmental Health Hazard Assessment – Public Health Goals
- Health Canada – Guidelines for Canadian Drinking Water Quality
- European Food Safety Authority | EFSA – Scientific Output Publications
- World Health Organization – Drinking Water Quality Guidelines, International Agency for Research on Cancer (IARC) Monographs
- European Commission – Joint Research Centre (JRC) Publications Repository
- European Chemicals Agency (ECHA) – Risk Assessments

Assessments from other governmental agencies were included when those were identified from the reference lists of large PFAS reviews or risk assessments found in the peer-reviewed literature. These included assessments from:

- Specific U.S. state agencies
- French Agency for Food, Environmental and Occupational Health and Safety | ANSES
- Danish Environmental Protection Agency
- Swedish Environmental Protection Agency
- Dutch National Institute for Public Health and the Environment | RIVM
- German Environment Agency | The UBA

Targeted PFAS chemicals with no TRVs identified using the described methods were also searched on the U.S. Environmental Protection Agency's (EPA) CompTox Chemicals Dashboard for hazard and risk values.

Additionally, gray literature sources for hazard data were searched including EPA's Comprehensive PFAS Dashboard and ECHA's Chemicals Database. The Comprehensive PFAS Dashboard includes an overview of the mammalian bioassay and epidemiological literature related to human health risk assessment for thousands of PFAS chemicals identified from the EPA's PFAS Systematic Evidence Maps (SEMs) and completed EPA assessments. ECHA's Chemicals Database includes animal toxicity data in chemical

dossiers submitted to ECHA under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation.

3.1.2. Peer-Reviewed Literature Search

We performed a peer-reviewed literature search using PubMed and Web of Science to identify primary and secondary data sources relevant for hazard, dose-response, exposure, and human health risk assessment for the targeted chemicals. Search terms and date limits specific for each chemical can be found in Supplemental File C. Hazard and dose-response terms were searched for the last 20 years (2004–2024) for each chemical, except for chemicals with existing hazard assessments from the EPA, which were searched from the year of last search in those assessments. Consumer product exposure terms were searched for the last 20 years (2004–2024) for each chemical. General background exposure terms were searched for the last 5 years (2019–2024) for 6:2 FTOH, 8:2 FTOH, perfluorooctanesulfonamide (PFOSA), DFE, and TFE and the last 3 years (2021–2024) for chemicals with substantial information available for background exposure (perfluorobutanoic acid [PFBA], perfluoroheptanoic acid [PFHpA], perfluorohexanoic acid [PFHxA], perfluorobutanesulfonic acid [PFBS], and APFO).

After deduplication, 2,617 potentially relevant references were identified (Figure 1). According to the Populations, Exposures, Comparators, and Outcomes (PECO) criteria (Supplemental File C), references were screened for relevance by title and abstract using DistillerSR (Evidence Partners, 2024). There were 968 references considered relevant after title-and-abstract screening. A cursory full-text pre-screen excluded 17 references for one of the following reasons: inability to obtain the full text, non-English language article, conference abstract, opinion article, or duplicate reference. During full-text screening, application of the PECO criteria determined that another 71 references were excluded as not relevant to the assessment, resulting in 880 references considered relevant after full-text screening. Of these, 473 were categorized as lower priority, while 407 were categorized as higher priority for containing useful data specific to completing this screening-level human health risk assessment. The categorization of higher versus lower priority was performed by CPSC staff according to their subject matter expertise and experience. While the lower priority references contained less useful information related to completing quantitative assessments, they could be potentially used in the future to better characterize distributions. Of the 407 higher-priority references, 238 were relevant to hazard and dose-response assessment and 327 were relevant to exposure assessment, with some relevant to both. PECO relevance was confirmed for all prioritized references and then tagged for additional study details.

Several expert-identified reviews and studies found outside the literature search were also considered and included in the assessment.

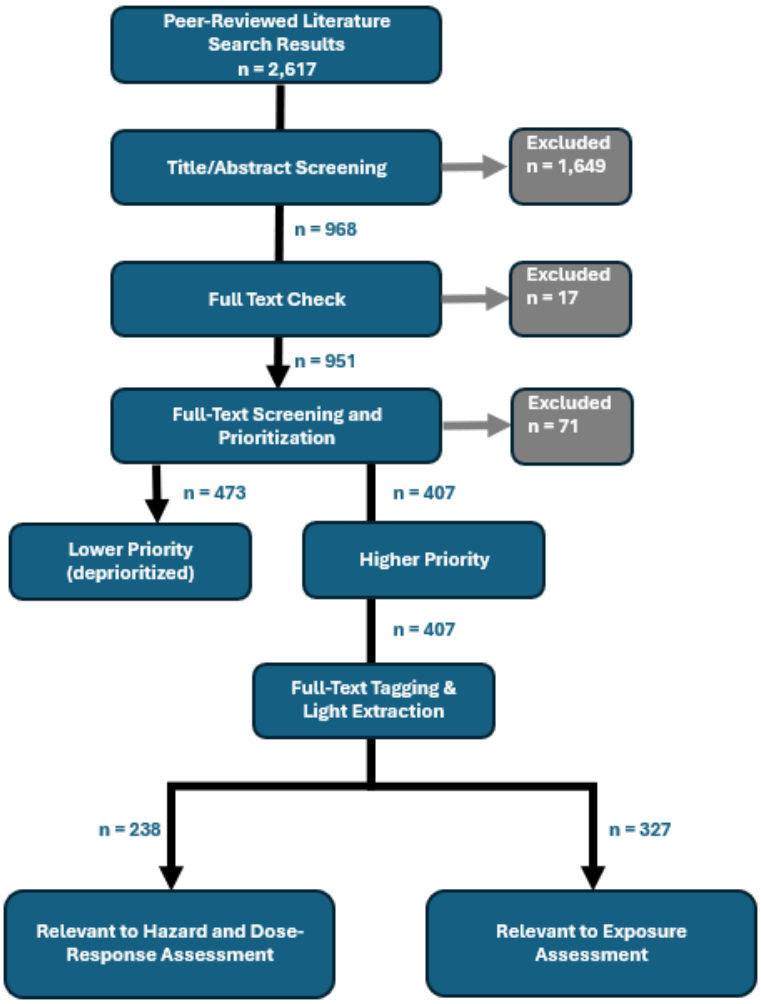

Figure 1. Peer-Reviewed Literature Flow.

3.2. Hazard Identification and TRV Derivation

For hazard assessment, we considered both hazard identification and dose-response assessment wherein (i) hazard identification describes the types of health effects caused by a given chemical, including weight of evidence considerations such as mode of action (MOA), human relevance of effects observed in experimental animals, and the dose/route of exposure associated with different health effects and (ii) dose-response assessment describes the relationship between the amount of exposure and the observed health effect (e.g., incidence and severity at a given level of exposure).

For this report, we chose to focus on noncancer endpoints because of the limitations in MOA for the data-poor chemicals in this assessment. Therefore, all further steps in this assessment focus on the development of noncancer TRVs. Given the MOA information needed to justify development of a cancer TRV, the lack of mechanistic data at this time does not support development of such a TRV. However, as more information about how

this chemical, or this chemical's subclass works, development of cancer TRVs will be possible (U.S. EPA, 2005).

To identify hazards associated with each chemical, the results of the literature search were screened in a tiered manner. First, chemicals that had an existing TRV from an authoritative agency were identified. No further steps were taken for these chemicals – the TRV was extracted and the distribution (described in Section 3.4.2) was parameterized. Next, chemicals for which risk assessments were present but no authoritative TRV was published were identified. In addition, toxicity studies and read-across methodologies for these chemicals were also identified. Animal toxicity data were obtained from subchronic, chronic, developmental, and multigenerational exposure studies, and adverse effects of short-term exposure were also considered given that some of these chemicals are data poor. Adverse effects of acute exposure were evaluated only for DFE and TFE as described in Supplemental File B. The EPA IRIS definitions were used for categorizing studies as short-term exposure (more than 24 hours up to 30 days), subchronic exposure (more than 30 days up to approximately 90 days in typically used laboratory animal species), or chronic exposure (more than approximately 90 days to 2 years in typically used laboratory animal species). Human epidemiologic evidence was also evaluated and considered during hazard assessment.

From the non-quantitative hazard assessments, screening-level risk assessments, and repeated dose toxicity studies providing potential PODs, the original data were used to model a benchmark dose lower confidence limit (BMDL). If the data did not pass statistical checks for BMD modeling, the no-observed-adverse-effect level (NOAEL) or lowest-observed-adverse-effect level (LOAEL) were used as the POD. Uncertainty factors (UFs) were applied based on study characteristics (U.S. EPA, 2014). Specifically, default values were used: for intraspecies variability, a UF of 10 was applied (UFH); for interspecies variability, a UF of 10 was applied (UFA); for subchronic to chronic extrapolation, a UF of 3 was applied (UFS); and lastly, if a LOAEL was used in place of a NOAEL, a UF of 10 was applied (UFL). In addition, 6:2 FTOH, 8:2 FTOH, PFHpA, and PFOSA were assigned TRVs based on chemical similarity using chemical read-across (Lizarraga et al., 2023). Finally, where applicable, TRVs were converted from an oral RfD (mg/kg/day) to a reference air concentration (RfC; mg/m^3) when inhalation was identified as a major route of exposure for consumers (i.e., for FTOHs). For these chemicals, the recommended adult-specific body weight and inhalation rate (U.S. EPA, 2011) were used for the conversion, assuming an inhalation absorption fraction of 1.

Following the calculation of candidate RfDs and RfCs, a single TRV was selected when enough data existed to support a choice. Specifically, TRVs were considered depending on (i) consistency of effect according to the chemical database, (ii) study characteristics

(i.e., chronic versus subchronic, rodent versus human), and (iii) aggregate uncertainty in the estimate. To capture uncertainty in the estimate of these chemicals, the distributions were parameterized by a log normal distribution as the right-skew of the distribution results in an overall probability of a lower number being chosen as the risk estimate (Section 3.4.3, ICF, 2025).

For chemicals for which high uncertainty in the estimate was coupled with a lack of consistency in the estimates from chemical-specific data, no singular TRV candidate was chosen. Rather, a distribution was parameterized from only the lower and upper bounds with no defined central tendency value chosen (Section 3.4.4).

3.3. Exposure

3.3.1. Overview of Approaches to Estimate Exposure

An exposure assessment estimates or measures the magnitude, frequency, and duration of exposure to an agent (e.g., chemical substance) and describes the population exposed (U.S. EPA, 2019b). Several approaches can be used to estimate exposure, wherein the approach used is dependent on data availability, the specific exposure scenario, and the purpose of the assessment, among other factors. The three approaches used to estimate exposure in this report are briefly described below, with additional details described elsewhere (ICF, 2024):

1. Mechanistic models: use of mechanistic models based on first principles to estimate indoor environmental concentrations and/or doses associated with consumer products used in indoor or quasi-indoor environments. Exposure scenarios (i.e., source-pathway-receptor) are first developed to describe how exposure occurs.

2. Empirical measurements: includes (i) use of chemical migration measurements from products to people to estimate contact (direct) consumer exposure, (ii) use of chemical emissions measurements from products to indoor environments to estimate mediated (indirect) consumer exposure, or (iii) use of occurrence data in various environmental media for contact or mediated exposure. These measurements are used with simple equations to estimate dose.

3. Reverse dosimetry: use of occurrence data in biological matrices and chemical-specific toxicokinetic data to estimate the dose that would be consistent with the measured biomonitoring level. This approach estimates total dose for all sources and pathways to which a person is exposed.

3.3.2. Mechanistic Models

Mechanistic models are used to estimate exposure by first defining the exposure scenarios of interest, wherein the source, pathway, and receptor are characterized. Model equations are based on well-established mechanistic processes informed by

physicochemical properties, and inputs include source inputs (physicochemical properties and consumer product/material properties), environmental inputs (room volume, air exchange rate), and population inputs (exposure factors, activity patterns).

3.3.2.1. Modeling Tool

Several exposure modeling tools are available that estimate exposure to chemicals from consumer products, all with well-established documentation and/or have been peer reviewed. For this report, both consumer products and articles are considered as sources. Products are consumable sources with specific times and frequencies of use (e.g., carpet cleaner), whereas articles are sources that are continuously present and releasing chemicals into the home (e.g., carpets).

We used the EPA's Stochastic Human Exposure and Dose Simulation High-Throughput (SHEDS-HT) model version 0.1.10 (U.S. EPA, 2024c) to provide screening-level estimates of exposure. SHEDS-HT is a probabilistic model that estimates chemical exposure in a population from the three mediated and two contact exposure pathways listed below.

1. Ingestion of indoor dust: This mediated pathway models incidental ingestion of settled dust (floor dust, surface dust).
2. Inhalation of particle dust: This mediated pathway models inhalation of airborne particulates, followed by absorption in the gastrointestinal tract.
3. Inhalation of gas: This mediated pathway models inhalation of gas, followed by lung absorption.
4. Dermal: This contact pathway models direct contact of the product with the skin, with chemical migration into the skin over time. SHEDS-HT version 0.1.10 does not model direct contact with articles, however, this pathway is considered in the empirical approach.
5. Mouthing/oral: This contact pathway models direct product-to-mouth contact, where the chemical migrates into saliva.

The sources of exposure are either products or articles and are denoted as product use categories (PUCs). Within each PUC, there are also different formulations (e.g., liquid, aerosol) and within each formulation, there are different brands (which provide the specific chemical composition). The outputs of SHEDS-HT model runs are concentrations and doses reported as distributions across the population. While SHEDS-HT simulates only 1 day of exposure, the population mean and standard deviation can be used as a surrogate for chronic exposure because SHEDS-HT simulates 1-day exposures of many persons by randomly sampling inputs from user-specified distributions. SHEDS-HT examines 1 day per simulated person, but the day examined is not necessarily the day a

product is used (if not, then the person is exposed to residual chemical from past uses). Each person is independent of all others, which implies they all live in different houses. Each person is randomly assigned an age and other properties, including whether they use or do not use each product in the house. If a product is used in the house, the use frequency is checked to determine whether the day being modeled is a day that product is used. If so, then both direct and indirect exposure occur. If the product is used in that house but not on that day, then only indirect exposure occurs. The amount of indirect exposure depends on the number of days since the product was last used. If the person being modeled is not a user (which is often the case for a young child) then a check is made if someone else in that house (usually a parent) uses that product. If so, then the person being modeled receives indirect exposure (but no direct exposure). If no one in that house uses that product, then the exposure is assumed to be zero.

The use frequency applies only to the houses that use the product (i.e., use prevalence of 1). If the use frequency is 365 times per year or more, then all days are usage days (if that product is used at all). A use frequency over 365 per year can result in multiple uses on the same day, in which case the exposure from one usage event is multiplied by that number. In most cases, the use frequency is fewer than 365 per year. For example, if a product is used once per week (i.e., use frequency = 52 per year) and the use prevalence is 0.5, then in a large sample of persons, half will not use that product and the other half will have a 1/7 chance of being a usage day, another 1/7 chance of yesterday being a usage day, up to 6 days before being the most recent usage day. Each person is randomly assigned to 1 of the 7 days, with each day having a 1/7 probability. For simplicity, if on a usage day the exposure is 7 mg/kg/day and exposure decreases by one unit each day, then in a large sample, 1/7 of the users would have an exposure of 7 mg/kg/day, another 1/7 would have an exposure of 6 mg/kg/day, down to 1/7 having an exposure of 1 mg/kg/day. Note that the 50% of simulated persons who do not have the product in the house would have an exposure of zero. If a model is considered that follows a user over 1 year with the person regularly using that product each week, then 1/7 of the days would have an exposure of 7 mg/kg/day, another 1/7 of the days would have an exposure of 6 mg/kg/day (because the product was used yesterday but not today), another 1/7 of the days would have an exposure of 5 mg/kg/day, down to 1/7 having an exposure of 1 mg/kg/day. The next day the cycle would repeat. Therefore, the average exposure over the year in this longitudinal model would equal the average exposure (of the users only) in the cross-sectional SHEDS-HT model.

3.3.2.2. Input Data

Multiple input files are needed to run SHEDS-HT but most of the default input files (e.g., population input file, which is used to assign age and gender randomly using probabilities consistent with the general population) can be used as is. Four of the default input files

were reviewed and revised: (i) chemical properties file, which contains chemical-specific properties such as molecular weight, half-life in air, and skin permeability coefficient; (ii) source chemicals file, which contains parameters that are dependent on both the source and the specific chemical – this file provides information on which products a chemical is found in and their weight fraction, which can be provided as a point value or as a range; (iii) source variables file, which provides information on the habits and practices of people, such as duration of use of a product, fraction of households with the product, and frequency of product use – these values do not depend on the chemical; and (iv) source scenarios file, which allocates the mass of product that goes to each compartment, such as fraction of mass going to surfaces during use versus fraction of mass being ingested during use for products – these values are also independent of the chemical.

The chemical properties file was updated with data from the EPA CompTox Chemicals Dashboard for the targeted PFAS chemicals. To populate the source chemicals file, weight fraction data for 6:2 FTOH, 8:2 FTOH, PFBA, PFHxA, PFHpA, and PFBS were pulled from two sources – the Holder et al. (2023) SEM and a review by Dewapriya et al. (2023). Because PFOSA was not a targeted chemical in the two SEMs, we reviewed the literature search results for studies tagged with PFOSA data and extracted the results for all relevant PFAS chemicals. Each chemical-product data set was then fit to a log normal distribution to obtain geometric mean and 95th percentile weight fractions. The individual consumer products were crosswalked to a SHEDS-HT PUC or if there was no comparable PUC, a new one was created. Pooled geometric means (GMs) and 95th percentiles (P95s) were calculated for each chemical-PUC combination for which the individual GM and P95 were weighted by the number of samples. For the SHEDS-HT runs, to prevent a weight fraction being randomly drawn that was outside the range of the original data, we assumed a uniform distribution between the 5th and 95th percentiles. For DFE and TFE, there were no databases identified with consumer product information; however, both chemicals are part of the default input files. The inputs available for DFE and TFE were used as is, with one modification. Electronics cleaner (e.g., air duster) was initially only included under TFE but since commercial products are known to contain DFE, we added electronics cleaner to DFE inputs. In addition to weight fraction data, the source chemicals file also contains the y_0 parameter for articles, which is defined as the gas-phase concentration in the boundary layer of air next to the surface of the article and is assumed to be in equilibrium with the material. y_0 was estimated using physicochemical properties (see Supplemental File E for derivation) to give an upper bound (and likely overestimate and therefore conservative measure) of y_0.

For the source variables and source scenarios files, the default data available for products are based on the EPA's curation of existing data in the literature to characterize usage (i.e., prevalence, frequency, and magnitude). All source parameters were reviewed

and updated as needed based on professional judgment. Articles are not currently included in the default input files and therefore article parameters (e.g., surface area, home prevalence) were based on professional judgment. The updated SHEDS-HT input files are available in Supplemental File E.

3.3.3. Empirical/Environmental Monitoring Data

Empirical measurements are used to estimate pathway-specific exposures depending on the type of empirical data collected. In this report, nine pathways are considered. Inhalation exposures determined from personal air monitoring data or product emission data were not considered due to lack of data.

3.3.3.1. Inhalation of Indoor/Outdoor Air

The inhalation absorbed dose is given by:

$$AD_{inh} = \frac{(C_a \times 10^{-6}) \times Inh \times f_{home/outdoor} \times f_{abs\_inh}}{BW} \quad \text{(Eq. 1)}$$

Where:

AD_{inh} = inhalation absorbed dose (mg/kg/day)
C_a = concentration of chemical in gas phase and attached to airborne particles (ng/m^3)
Inh = inhalation rate (m^3/day)
$f_{home/outdoor}$ = fraction of time spent in home or away from home (-)
f_{abs_inh} = absorption fraction for inhalation (-)
BW = body weight (kg)
10^{-6} = (mg/ng)

3.3.3.2. Ingestion of Drinking Water

Exposure due to drinking water ingestion is given by:

$$AD_{ing} = \frac{(C_{dw} \times 10^{-6}) \times (consR \times 10^{-3}) \times f_{abs\_ing}}{BW} \quad \text{(Eq. 2)}$$

Where:

AD_{ing} = ingestion absorbed dose (mg/kg/day)
C_{dw} = concentration of chemical in drinking water (ng/L)
$consR$ = water consumption rate (mL/day)
f_{abs_ing} = absorption fraction for ingestion (-)
BW = body weight (kg)
10^{-6} = (mg/ng)
10^{-3} = (L/mL)

3.3.3.3. Ingestion of Soil

Exposure from incidental soil ingestion is given by:

$$AD_{ing} = \frac{(C_{soil} \times 10^{-6}) \times (soil\_Ing \times 10^{-3}) \times f_{abs\_ing}}{BW} \quad \text{(Eq. 3)}$$

Where:

AD_{ing} = ingestion absorbed dose (mg/kg/day)
C_{soil} = concentration of chemical in soil (ng/g)
$soil\_Ing$ = soil ingestion rate (mg/day)
f_{abs_ing} = absorption fraction for ingestion (-)
BW = body weight (kg)
10^{-6} = (mg/ng)
10^{-3} = (g/mg)

3.3.3.4. Dermal Deposition from Gas Phase

The dermal absorbed dose from gas-phase deposition is given by (Mitro et al., 2016; Pelletier et al., 2017):

$$AD_{der} = \frac{(C_g \times 10^{-6}) \times (k_{p-g} \times 10^{-2} \times 24) \times BSA \times f_{home}}{BW} \quad \text{(Eq. 4)}$$

Where:

AD_{der} = dermally absorbed dose (mg/kg/day)
C_g = gas-phase chemical concentration (ng/m^3)
k_{p-g} = indoor air transdermal permeability coefficient (cm/hr)
BSA = human body surface area (m^2)
f_{home} = fraction of time spent in home (-)
BW = body weight (kg)
10^{-6} = (mg/ng)
10^{-2} = (m/cm)
24 = (hr/day)

The transdermal permeability coefficient is calculated with the following equations (further details and original sources cited in Pelletier et al., 2017):

$$k_{p\_cw} = 10\text{^}(0.7 \times \log K_{ow} - 0.0722 \times MW^{\frac{2}{3}} - 5.252) \times 3{,}600 \quad \text{(Eq. 5)}$$

$$B = \frac{k_{p\_cw} \times MW^{0.5}}{2.6} \quad \text{(Eq. 6)}$$

$$k_{p\_w} = \frac{k_{p\_cw}}{1+B} \quad \text{(Eq. 7)}$$

$$k_{p\_b} = \frac{k_{p\_w}}{K_{aw}} \quad \text{(Eq. 8)}$$

$$k_{p\_g} = \frac{1}{\frac{1}{V_d} + \frac{1}{k_{p\_b}}} \quad \text{(Eq. 9)}$$

Where:

k_{p_cw} = water phase permeability coefficient through stratum corneum (cm/hr)
K_{ow} = octanol-water partition coefficient (-)
MW = molecular weight of chemical (g/mol)
B = ratio of stratum corneum to viable epidermis permeabilities (-)
k_{p_w} = water phase permeability through stratum corneum and viable epidermis (cm/hr)
k_{p_b} = gas phase permeability coefficient through skin surface (cm/hr)
K_{aw} = air-water partition coefficient (-)
k_{p_g} = transdermal permeability coefficient (cm/hr)
V_d = air-to-skin deposition velocity (cm/hr)

If K_{aw} is not known, it can be calculated using other input parameters:

$$K_{aw} = \frac{K_{ow}}{K_{oa}} = \frac{H}{R \times T} \quad \text{(Eq. 10)}$$

Where:

K_{aw} = air-water partition coefficient (-)
K_{ow} = octanol-water partition coefficient (-)
K_{oa} = octanol-air partition coefficient (-)
H = Henry's law constant (Pa m^3/mol)
R = universal gas constant = 8.314 Pa m^3 / (mol K)
T = temperature (K)

3.3.3.5. Ingestion of Indoor Dust

The indoor dust ingestion absorbed dose is given by:

$$AD_{ing} = \frac{X_{dust} \times dust\_Ing \times f_{abs\_ing}}{BW} \quad \text{(Eq. 11)}$$

Where:

AD_{ing} = ingestion absorbed dose (mg/kg/day)
X_{dust} = chemical mass fraction in settled dust (-)
$dust\_Ing$ = dust ingestion rate (mg/day)

f_{abs_ing} = absorption fraction for ingestion (-)
BW = body weight (kg)

The dust ingestion rate in the equation above reflects both (i) mouthing of dusty objects such as plush toys and (ii) first getting dust on the hands from surfaces such flooring and then transferring by hand-to-mouth contact.

3.3.3.6. Dermal Absorption of Dust

Exposure due to dermal absorption of dust is typically not estimated because of the difficulty of quantification and its large interpersonal variability. For example, it may be higher for mouthing infants and toddlers and lower for adults. As part of a previous call order under this contract (Call Order No. 61320622F2012), we previously estimated dermal absorption of dust by considering this pathway as a two-step process in which the person first contacts the settled dust with their hands, followed by chemical leaching from the dust into the biofilm (sweat, sebum) on the skin surface, and subsequent absorption. Further details are discussed in ICF (2024). While this approach focuses on hands, it could be expanded to other body parts (e.g., bottoms of feet, arms, legs) in the future. The relevant equations are provided below.

To avoid double counting of dust that is ingested via hand-to-mouth transfer versus dust that stays on the hand and is absorbed dermally, we first calculated the rate of dust ingested from mouthing hands and the rate of dust accumulating on the hands. The rate of dust mass ingested from the hands is:

$$Ing_{hands} = Ing \times f_{ing\_htm} \quad \text{(Eq. 12)}$$

Where:

Ing_{hands} = dust ingestion rate due to hand-to-mouth transfer (mg/day)
Ing = dust ingestion rate (mg/day)
f_{ing_htm} = fraction of ingested dust due to hand-to-mouth transfer (-)

The rate of dust accumulating on the hands is estimated as:

$$Dust_{hands} = \frac{Ing_{hands}}{f_{hand\_ing}} \quad \text{(Eq. 13)}$$

Where:

$Dust_{hands}$ = rate of dust adhering to hands (mg/day)
Ing_{hands} = dust ingestion rate due to hand-to-mouth transfer (mg/day)
f_{hand_ing} = fraction of dust on hands that enters the mouth

The amount of dust picked up on the hands and available for dermal absorption is then given as:

$$Dust_{hands\_adj} = Dust_{hands} - Ing_{hands} \quad \text{(Eq. 14)}$$

Where:

$Dust_{hands\_adj}$ = rate of dust adhering to hands available for dermal absorption(mg/day)
$Dust_{hands}$ = rate of dust adhering to hands (mg/day)
Ing_{hands} = dust ingestion rate due to hand-to-mouth

The dermal absorbed dose from dust absorption is then given by:

$$AD_{der} = \frac{Dust_{hands\_adj} \times X_{dust} \times f_{abs\_derm}}{BW} \quad \text{(Eq. 15)}$$

Where:

AD_{der} = dermally absorbed dose (mg/kg/day)
$Dust_{hands\_adj}$ = rate of dust adhering to hands available for dermal absorption(mg/day)
X_{dust} = chemical mass fraction in settled dust (-)
f_{abs_derm} = absorption fraction for dermal (-)
BW = body weight (kg)

3.3.3.7. Direct Dermal Contact

Skin wipe data, which measures chemicals accumulated on skin surface over time and up until sampling, can be used to estimate direct dermal exposure using two methods: (i) fraction absorbed and (ii) permeability coefficient.

In the fraction-absorbed method, dose is given by (Tay et al., 2018):

$$AD_{der} = \frac{C_{hw} \times SA \times f_{abs\_derm} \times ED \times EF}{BW \times 24} \quad \text{(Eq. 16)}$$

Where:

AD_{der} = dermally absorbed dose (ng/kg/day)
C_{hw} = surface area normalized chemical mass of chemical in handwipes (ng/cm^2)
SA = hand skin surface area exposed per event (cm^2/event)
f_{abs_derm} = absorption fraction for dermal (-)
ED = exposure duration (hr/day), assumed to be 24 hr/day
EF = exposure frequency (event/day) assumed to be 1

BW = body weight (kg)
24 = (hr/day)

In the permeability coefficient method, dose is estimated as (Liu et al., 2017):

$$AD_{der} = \frac{k_{p-l} \times C_d \times SA \times ED}{BW} \quad \text{(Eq. 17)}$$

$$k_{p-l} = \frac{k_{p-w}}{K_{l-w}} \quad \text{(Eq. 18)}$$

$$C_d = \frac{C_{hw}}{\mathrm{h}} \quad \text{(Eq. 19)}$$

Where:

AD_{der} = dermally absorbed dose (ng/kg/day)
k_{p-l} = permeability coefficient of chemical from lipid to skin (cm/hr)
C_d = chemical concentration in skin lipid (ng/cm^3)
SA = hand skin surface area (cm^2)
ED = exposure duration (hr/day), assumed to be 24 hr/day
BW = body weight (kg)
k_{p-w} = permeability coefficient from water to skin (cm/hr)
K_{l-w} = partition coefficient between skin surface lipids and water (–), approximated with the octanol-water partition coefficient, K_{ow}
C_{hw} = surface area normalized chemical mass of chemical in handwipes (ng/cm^2)
h = thickness of skin surface lipid film (cm)

3.3.3.8. Mouthing

Mouthing by children is a natural and essential part of their development. Exposure due to mouthing (i.e., direct product-to-mouth contact) can be estimated using measured chemical migration rates from product to artificial saliva) as given by (Aurisano et al. 2022):

$$AD_{ing} = \frac{R_{mgr} \times A_{contact} \times t_m}{BW} \quad \text{(Eq. 20)}$$

Where:

AD_{ing} = ingestion absorbed dose (ng/kg/day)
R_{mgr} = migration rate of chemical to saliva (ng/cm^2/min)
$A_{contact}$ = mouthing contact area (cm^2)
t_m = mouthing duration per day (min/day)
BW = body weight (kg)

3.3.3.9. Background and Total Exposure

Background exposures that are not consumer product-related are first calculated by summing the exposures estimated from inhalation of outdoor air, drinking water ingestion, soil ingestion, and dietary ingestion. The last pathway, dietary ingestion, was not estimated de novo in this report because exposure values were already available from an authoritative source.

Total exposure is calculated as the sum of total background exposure and the exposures from the remaining pathways. In the case of direct dermal contact, when exposure can be calculated using two different approaches, we used the higher (more conservative) value.

3.3.3.10. Input Data for Exposures Estimated Using Empirical Measurements

Chemical monitoring data characterizing the occurrence of PFAS in indoor air, outdoor air, drinking water, soil, and indoor dust were primarily obtained from a SEM database (Holder et al., 2023). For chemicals that were not part of the SEM, secondary data were extracted from existing assessments when available. If there were fewer than five data sets in the SEM for a chemical-media combination, the results of the peer-reviewed literature search described in Section 3.1.2 were reviewed for relevant data. No data sets were identified in the SEM, in existing assessments, or from the peer-reviewed literature search for (i) 6:2 FTOH and 8:2 FTOH in drinking water, (ii) 6:2 FTOH and 8:2 FTOH in food, (iii) migration rates from products into saliva, and (iv) skin wipe data; therefore, a targeted search was performed.

All other inputs for the empirical approach are shown in Table 2. In some instances, values were selected using professional judgment, wherein the knowledge and experience of a subject matter expert were used to make an informed decision.

Table 2. Input Values Used to Calculate Dose from Empirical Measurements.

Symbol	Variable	Value	Value (Reference)
Chemical-specific Inputs			
MW	Molecular weight of chemical	Chemical-specific (-)	U.S. EPA CompTox Chemicals Dashboard
K_{ow}	Octanol-water partition coefficient	Chemical-specific (-)	U.S. EPA CompTox Chemicals Dashboard
K_{oa}	Octanol-air partition coefficient	Chemical-specific (-)	U.S. EPA CompTox Chemicals Dashboard
H	Henry's law constant	Chemical-specific (-)	U.S. EPA CompTox Chemicals Dashboard
Exposure Factors[a]			
BW	Body weight	7.78, 11.3, 17.8, 29.3, 54.2, 67.6, 80.0 kg	U.S. EPA (2011)

Symbol	Variable	Value	Value (Reference)
Inh	Inhalation rate	5.4, 8.0, 10.1, 12.0, 15.2, 16.3, 15.4 m^3/day	U.S. EPA (2011)
$soil\_Ing$	Soil ingestion rate	25, 40, 40, 30, 14, 10, 10 mg/day	U.S. EPA (2017)
$dust\_Ing$	Dust ingestion rate	30, 50, 40, 30, 22, 20, 20 mg/day	U.S. EPA (2017)
$consR$	Drinking water consumption rate	628, 300, 416, 565, 767, 1,068, 1,575 mL/day	U.S. EPA (2019a)
f_{home}	Fraction of time spent in home	0.89, 0.82, 0.77, 0.74, 0.74, 0.71, 0.73	U.S. EPA (2023a)
$f_{outdoor}$	Fraction of time spent away from home	0.11, 0.18, 0.23, 0.26, 0.26, 0.29, 0.27	U.S. EPA (2023a)
BSA	Human body surface area	0.40, 0.53, 0.76, 1.08, 1.59, 1.84, 2.00 m^2	U.S. EPA (2011)
Mouthing Inputs			
$A_{contact}$	Mouthing contact area	10 cm^2	Professional judgment
t_m	Mouthing duration per day	37, 47.4, 70.1 min/day for <1 yr, 1–2 yrs, 3–5 yrs, respectively	Greene (2002)
Direct Dermal Inputs			
f_{abs_derm2}	Absorption fraction for dermal	0.5 for 6:2 FTOH[b] 0.5 for 8:2 FTOH[b] 0.013 for PFOSA 0.694 for PFBA[c] 0.288 for PFHpA 0.364 for PFHxA 0.487 for PFBS	Danish EPA (2022) Danish EPA (2022) Ragnarsdottir et al. (2024) - PFOS used as surrogate Estimated in this report Ragnarsdottir et al. (2024) Ragnarsdottir et al. (2024) Ragnarsdottir et al. (2024)
k_{p-w}	Permeability coefficient of chemical from water to skin[d]	7.06×10^{-5} cm/hr for PFHpA 2.54×10^{-5} cm/hr for PFHxA 1.08×10^{-5} cm/hr for PFBS	Ragnarsdottir et al. (2024)
h	Thickness of skin surface lipid film	1.3 cm	Cao et al. (2019)
Other Inputs			
f_{abs_inh}	Absorption fraction for inhalation	1	Professional judgment
f_{abs_ing}	Absorption fraction for ingestion	1	Professional judgment
f_{ing_htm}	Fraction of ingested dust due to hand-to-mouth transfer	0.75	Professional judgment

Symbol	Variable	Value	Value (Reference)
$f_{hand_{ing}}$	Fraction of dust on hands that enters the mouth	0.05[e]	Professional judgment
V_d	Air-to-skin deposition velocity	600 cm/hr	Mitro et al. (2016)

[a]When multiple values are given, these correspond to age-specific inputs for <1 year, 1–2 years, 3–5 years, 6–10 years, 11–15 years, 16–20 years, and 21+ years. The median value was used for body weight.
[b]No data were available for dermal absorption fraction for fluorotelomer alcohols. A value of 0.5 was used based on Danish EPA (2022) which noted, "In an early study by industry scientists, it was assumed that dermal absorption of PFASs by contact to children's clothing would be 50% of the content."
[c]Dermal absorption fraction for PFBA estimated in this report based on a regression equation for perfluoroalkyl carboxylic acids data from Ragnarsdottir et al. (2024) versus chain length.
[d]Ragnarsdottir et al. (2024) reported permeability coefficients from methanol to skin for human in vitro 3D human skin equivalent models, which were converted to permeability coefficients from water to skin using K_{ow}.
[e]Fraction of dust on hands that enters the mouth is assumed to be 0.05 because typical behavior (e.g., thumb sucking) involves one finger. Each finger has roughly 10% of the surface area of one hand, and usually just one hand is mouthed, making 5% of the surface area of both hands.

3.3.4. Reverse Dosimetry

PFAS intakes can be estimated using chemical measurements in human biological matrices (i.e., biomonitoring data). Examples of human biomatrices include whole blood, plasma, serum, urine, and breast milk, among others. Depending on the chemical and matrix, different methods and equations are available to calculate daily intake (UC, 2021).

3.3.4.1. Key Equations

For PFAS chemicals, several studies use a simple one-compartment, first-order model to estimate daily intake dose. In a scoping assessment of toxicokinetic models used for PFAS chemicals, East et al. (2023) found that most analyses (50 of the 92 papers) used a one-compartment model, primarily focusing on PFOA and PFOS. Blood serum (or whole blood) is modeled as the compartment and PFAS concentration in blood is predicted using:

$$\frac{dC_s}{dt} = \frac{\mathrm{D}}{V_D} - k_e \times C_s \qquad \text{(Eq. 21)}$$

Where:

C_s = concentration in the serum (ng/mL)
D = daily intake dose (ng/kg/day)
V_D = volume of distribution (mL/kg)
k_e = elimination rate (1/day)

The elimination rate constant can be calculated using half-life values:

$$k_e = \frac{\ln(2)}{t_{1/2}} \qquad \text{(Eq. 22)}$$

Where:

k_e = elimination rate (1/day)
$t_{1/2}$ = half-life (day)

Assuming constant V_D and k_e, and steady state conditions gives:

$$C_s = \frac{\mathrm{D}}{k_e \times V_D} \quad \text{(Eq. 23)}$$

Equation 23 can then be rearranged to calculate daily intake dose D:

$$D = C_s \times k_e \times V_D \quad \text{(Eq. 24)}$$

3.3.4.2. Input Data

The present work used whole blood or serum data that were already extracted or identified in existing assessments and reviews. The use of whole blood or serum data was dependent on the chemical, with Poothong et al. (2017) noting that whole blood concentrations were more appropriate to use for PFHxA and PFOSA due to their strong partitioning.

Biomonitoring data for PFOSA, PFBA, PFHpA, PFHxA, and PFBS were extracted from two existing assessments (ATSDR 2021, EFSA 2020) and one peer-reviewed article that summarized biomonitoring data (Liu et al., 2024b). Umbilical cord data were used as a surrogate for infants. The most recent National Health and Nutrition Examination Survey (NHANES) cycle of available PFAS data was also reviewed for PFOSA (2011–2012; children 2013–2014), PFHpA (2011–2014; children 2013–2014), PFHxA (2017–2018), and PFBS (2011–2014; children 2013–2014), but the reported medians were all below the limit of detection (CDC, 2025). No biomonitoring data were available for 6:2 FTOH or 8:2 FTOH as these chemicals rapidly biotransform into other PFAS chemicals. There were also no NHANES biomonitoring data available for DFE or TFE. Concentrations of DFE and TFE in human blood identified in the literature corresponded to experimental or acute scenarios related to huffing (see Supplemental File B) and were therefore not representative of chronic exposures to traditional use of consumer products due to relatively quick clearance. The lack of data representative of chronic exposure to DFE and TFE from traditional use of consumer products represents a data gap, especially given that both chemicals have been identified in consumer products. All biomonitoring data used can be found in Supplemental File G.

Half-life values were identified from existing assessments and in instances for which separate half-life values were reported for males, females, and combined males and females, the combined value was extracted. For PFOSA, no measured half-life values were

identified and therefore the modeled half-life value from the National Toxicology Program's Integrated Chemical Environment (ICE) tool (PBPK module) was used. Limited data are available for volume of distribution values. Dawson et al. (2023) proposed using a value of 0.202 L/kg for all the PFAS chemicals they evaluated, which was the median across approximately 100 PFAS-by-species measurements. The final half-life values used are shown in Table 3.

Table 3. Half-Life Values Used in Simple One-Compartment First-Order Model.

Chemical	Half-Life Value	Measured or Modeled	Reference
PFOSA	99.65 hrs	Modeled	ICE PBPK tool
PFBA	74.63 hrs	Measured in serum, males and females	Chang et al. (2008)
PFHpA	0.17 yrs	Measured in serum	Xu et al. (2020)
PFHxA	275 hrs	Measured in whole blood, males and females	U.S. EPA. (2023b), calculated using data of Nilsson et al. (2013)
PFBS	0.12 yrs	Measured in serum	Xu et al. (2020)

3.4. Risk

3.4.1. Risk Characterization Approach

Human health risk assessment is the process of characterizing the impacts to human health following exposures to given chemical(s) and source(s). The information derived from hazard and exposure assessments are used to characterize risk, which includes both a quantitative description of the risk(s) associated with exposure(s) and a quantitative or qualitative description of the associated uncertainties.

To characterize risk, we calculated several HQs that compare measured or estimated levels of real-world exposure to the TRVs.

$$HQ = \frac{Exposure}{TRV} \quad \text{(Eq. 25)}$$

For a traditional risk assessment, the HQ is typically a deterministic value for which a single point estimate is used for exposure and a single point estimate is used for the TRV. It is interpreted relative to a value of 1: if HQ ≤ 1, no adverse effects are expected, but if HQ > 1, then sensitive populations may begin to experience mild effects, with the likelihood of an effect and potential severity of the effect increasing as the HQ increases.

Given the limitations in the hazard data for some of these chemicals (as described in Section 4.1), rather than calculating a traditional single point HQ, we chose to perform a

probabilistic screening-level risk assessment following the approach developed under a previous call order under this contract (Call Order No. 61320623F2030) and described in ICF (2025). Briefly, this approach included developing parameters to describe the probability distributions of exposure and hazard and then using these distributions to estimate the cumulative probability (Pr) for HQs > 1. This choice of methodology allows us to account for the differences in certainty in the hazard estimate by differentially parameterizing the distribution based on differences in the strength of the data sources for each chemical. Further, these types of calculations can provide insight into where more chemical-specific information can strengthen the risk estimate by reducing uncertainty. Below, we detail how different types of TRV estimates can be parameterized and also discuss how to parameterize exposure distributions and calculate risk probabilities from these distributions.

3.4.2. TRV Distribution Parameterization, Authoritative Assessment

For the first group of chemicals for which TRVs were taken directly from an authoritative assessment, a normal distribution shape was chosen as we assumed that the TRV distribution should be equally sized on either side (Krithikadatta, 2014; U.S. EPA, 2002). In these cases, the population mean, or central tendency estimate (μ), is the published TRV and the 5th ($q_{0.05}$) and 95th ($q_{0.95}$) percentiles of the distribution are estimated as spanning one order of magnitude centered on the central tendency (i.e., the 5th percentile is equal to the mean divided by 3 and the 95th percentile is equal to the mean multiplied by 3). This distribution is based on the phrase in the definition of the RfD that it is a value with "uncertainty spanning perhaps an order of magnitude." (U.S. EPA, 2002).

To estimate the standard deviation σ we used the α-percentile equation for a normal distribution with mean μ and standard deviation σ:

$$q_\alpha = \mu + \sigma \times \Phi^{-1}(\alpha) \quad \text{(Eq. 26)}$$

Where α is the cumulative probability and Φ is the cumulative distribution function (CDF) for the standard normal distribution. From this equation, we solved for μ:

$$\mu = q_\alpha - \sigma \times \Phi^{-1}(\alpha) \quad \text{(Eq. 27)}$$

And form two estimates of μ using the $q_{0.05}$ and $q_{0.95}$ values. The two estimates are set equal to each other and solved for σ:

$$\mu_1 = q_{0.05} - \sigma \times \Phi^{-1}(0.05) = q_{0.95} - \sigma \times \Phi^{-1}(0.95) = \mu_2 \quad \text{(Eq. 28)}$$

$$\sigma \times \Phi^{-1}(0.95) - \sigma \times \Phi^{-1}(0.05) = q_{0.95} - q_{0.05} \quad \text{(Eq. 29)}$$

$$\sigma \times [\Phi^{-1}(0.95) - \Phi^{-1}(0.05)] = q_{0.95} - q_{0.05} \quad \text{(Eq. 30)}$$

$$\sigma = \frac{q_{0.95} - q_{0.05}}{\Phi^{-1}(0.95) - \Phi^{-1}(0.05)} \quad \text{(Eq. 31)}$$

3.4.3. TRV Distribution Parameterization, Single TRV Selected

For TRV estimates in which a single candidate TRV was selected, a log normal distribution shape was chosen to estimate the TRV distribution. Because these TRVs were screening level and did not undergo the same degree of scrutiny as those developed during an authoritative assessment, hazard was estimated with a right skew to bias the probability of the TRV towards the lower end of hazard. In these cases, the candidate TRV is estimated with the geometric mean ($q_{0.50}$), and $q_{0.05}$ and $q_{0.95}$ are estimated as the highest and lowest candidates. To determine $q_{0.50}$, $q_{0.05}$, and $q_{0.95}$, we assumed the log transformed values are normally distributed; we fit arithmetic mean and standard deviation in log space, found the 5th and 95th percentiles of that normal distribution, and then transformed back into regular space.

For this assessment, the arithmetic mean μ is calculated as:

$$\mu = \log(q_{0.50}) \quad \text{(Eq. 32)}$$

To estimate the standard deviation σ, we used the α-percentile equation for a log normal distribution with mean μ and standard deviation σ:

$$q_\alpha = \exp\left(\mu + \sigma \times \Phi^{-1}(\alpha)\right) \quad \text{(Eq. 33)}$$

Where α is the cumulative probability and Φ is the CDF for the standard normal distribution. From this equation, we solved for μ:

$$\mu = \log(q_\alpha) - \sigma \times \Phi^{-1}(\alpha) \quad \text{(Eq. 34)}$$

And form two estimates of μ using the $q_{0.05}$ and $q_{0.95}$ values. The two estimates are set equal to each other and we solved for σ:

$$\mu_1 = \log(q_{0.05}) - \sigma \times \Phi^{-1}(0.05) = \log(q_{0.95}) - \sigma \times \Phi^{-1}(0.95) = \mu_2 \quad \text{(Eq. 35)}$$

$$\sigma \times \Phi^{-1}(0.95) - \sigma \times \Phi^{-1}(0.05) = \log(q_{0.95}) - \log(q_{0.05}) \quad \text{(Eq. 36)}$$

$$\sigma \times [\Phi^{-1}(0.95) - \Phi^{-1}(0.05)] = \log(q_{0.95}) - \log(q_{0.05}) \quad \text{(Eq. 37)}$$

$$\sigma = \frac{\log(q_{0.95}) - \log(q_{0.05})}{\Phi^{-1}(0.95) - \Phi^{-1}(0.05)} \quad \text{(Eq. 38)}$$

3.4.4. TRV Distribution Parameterization, No TRV Selected

For TRV estimates in which no TRV was selected due to a lack of chemical-specific data and/or disagreement within the chemical database, a log normal distribution shape was chosen to estimate the TRV distribution. In these cases, $q_{0.05}$ and $q_{0.95}$ are estimated as the highest and lowest candidate TRV. The arithmetic mean μ is estimated by forming two estimates of μ using the $q_{0.05}$ and $q_{0.95}$ values in Equation (34) and averaging the results. The standard deviation σ is estimated with Equation (38).

$$\sigma = \frac{\log(q_{0.95}) - \log(q_{0.05})}{\Phi^{-1}(0.95) - \Phi^{-1}(0.05)} \quad \text{(Eq. 38)}$$

3.4.5. Exposure Distribution Parameterization

For exposure estimates, the geometric mean and 95th percentile values for exposure were estimated using each of the three approaches described in Section 3.3. To parameterize the distribution from these estimates, the mean μ, is calculated using Equation (32) from $q_{0.50}$. For the standard deviation σ, we used the α-percentile equation (Equation 27) for a log normal distribution and solved for σ as:

$$\sigma = \frac{\log(q_{0.95}) - \mu}{\Phi^{-1}(0.95)} \quad \text{(Eq. 39)}$$

3.4.6. Calculating Risk Probabilities from Distributions

For this probabilistic screening-level risk assessment, the metric evaluated is the proportion of the population for which the HQ > 1 (i.e., the cumulative probability [Pr] of an HQ > 1, Pr(HQ > 1)). Consistent with the approach developed in a previous call order under this contract (Call Order No. 61320623F2030) and on the work presented in Chiu and Slob (2015), we considered Pr values above 0.10 (i.e., more than 10%, or more than 10 out of 100) to be higher probability of chronic risk to human health.

To determine Pr(HQ > 1), two cases are considered:

- For cases in which both exposure and TRV are assumed to be log normally distributed, Pr(HQ > 1) is calculated from the CDF for a log normal distribution with:

$$\mu = \mu_{Exposure} - \mu_{TRV} \quad \text{(Eq. 40)}$$

and

$$\sigma = \sqrt{\sigma_{Exposure}^2 + \sigma_{TRV}^2} \quad \text{(Eq.41)}$$

- For cases in which exposure is assumed to be log normally distributed and TRV is assumed to be normally distributed, 100,000 exposure values are randomly

sampled from $LogNormal(\mu_{Exposure}, \sigma_{Exposure})$ and 100,000 TRV values are randomly sampled from $N(\mu_{TRV}, \sigma_{TRV})$. The values are divided to generate a simulated sample of 100,000 HQs. Pr(HQ > 1) is estimated as the proportion of sampled HQ values greater than 1.

4. Results and Discussion

4.1. Hazard

4.1.1. Summary of PFAS Health Effects

The health effects of selected PFAS chemicals have been reviewed and evaluated by many governmental agencies and other authoritative bodies. However, of the thousands of potential PFAS, a few dozen have been more closely investigated for their potential human health effects. In this report, the hazard assessment for each targeted PFAS chemical was preferentially based on prior assessments from the EPA and the Agency for Toxic Substances and Disease Registry (ATSDR) when available. Other comprehensive assessments were also used when available, including those from the European Food Safety Authority (EFSA) and from some environmental health agencies within the European Union. The existing assessments were supplemented with published literature searches conducted under this call order and expert-identified reviews and studies, including reports from the National Toxicology Program. Additionally, gray literature sources were identified from publicly available databases, including EPA's Comprehensive PFAS Dashboard and ECHA's Chemicals Database. The EPA found that mammalian toxicity or human epidemiologic studies are not available for the vast majority of PFAS chemicals searched as part of their systematic evidence mapping projects (Carlson et al., 2022; Shirke et al., 2024; Shirke et al., 2025).

There are many challenges for PFAS hazard assessment, including but not limited to, sparse information on toxicity for most PFAS chemicals, unknown human exposure levels to a mixture of PFAS chemicals, lack of concordance between animal data and human evidence, and species-specific differences in mechanisms of action and toxicokinetic factors, such as elimination half-lives (Anderson et al., 2022). Because health outcome profiles of emerging PFAS chemicals are generally consistent with legacy PFAS chemicals, data for PFOA and PFOS are frequently used to make read-across predictions of toxicity for chemicals with little to no toxicity data for human health risk assessment purposes.

Health effects and potency vary between PFAS chemicals because of the diversity of their chemical and physical properties; however, several common health effects and trends have been observed and are described in this section. Differences observed in relative potency are thought to be related to differences in elimination kinetics and

affinity for binding to specific receptor proteins (Fenton et al., 2021). Additionally, differences in metabolism may be involved when comparing toxicity of some PFAS chemicals. Many studies have shown that PFAAs are not metabolized in the body (ATSDR, 2021). They are excreted unchanged, primarily in the urine. However, some PFAS replacement chemicals, including precursors such as fluorotelomer alcohols and polyfluoroalkyl phosphate esters, are metabolized by animals and humans and biotransformed to PFAAs and other metabolites that may be more reactive, bioaccumulative, and/or toxic than the parent compound (EFSA, 2020).

The available animal evidence shows that PFAS chemicals are associated with health effects in several different organ systems (Fenton et al., 2021; ATSDR, 2021, EFSA, 2020). Repeated studies in rodents consistently report liver effects, including increases in liver weight, hepatocellular hypertrophy, and decreases in serum cholesterol and triglyceride levels. Other adverse effects commonly reported in animal studies include decreases in thyroid hormone levels, increases in fetal or neonatal mortality, and reductions in fetal weight or postnatal growth. Neurodevelopmental effects, increases in skeletal malformations or variations, delays in developmental milestones, immune suppression, changes in male reproductive parameters, and adverse effects in the kidney and thyroid have also been observed for several PFAS chemicals. Immunotoxicity and delayed mammary gland development have been observed at very low dose levels for PFOS and PFOA, respectively (Fenton et al., 2021).

Human epidemiologic literature on PFAS chemicals most strongly supports corresponding health effects in humans for immune function (e.g., reduced antibody response to vaccination), hepatic metabolism (e.g., increased cholesterol levels), thyroid function (e.g., altered thyroid hormone levels), and development (e.g., reduced birth weight) (Fenton et al., 2021; EFSA, 2020). Children may be more sensitive to PFAS exposures compared to adults based on higher body burdens and sensitive windows during development (Sunderland et al., 2019). Other studied outcomes in humans have suggestive associations with PFAS chemicals, including fatty liver disease, kidney disease, increases in uric acid, reproductive effects, pregnancy-induced hypertension, and offspring growth and adiposity (Fenton et al., 2021). The currently available evidence is mixed or inconclusive for other outcomes such as cardiovascular disease, diabetes, obesity, metabolic syndrome, and neurodevelopmental outcomes.

The mechanisms of PFAS toxicity are not well characterized given limitations of currently available information (Fenton et al., 2021, ATSDR, 2021). There is strong evidence that hepatotoxicity and other effects in laboratory animals involve activation of the nuclear receptor peroxisome proliferator–activated receptor-alpha (PPARα); however, observations of necrotic and degenerative effects in the liver of rodents and results from

studies in PPARα-null mice suggest that other pathways are also involved (ATSDR, 2021). Mechanistic studies have shown that PFAS chemicals can activate or perturb many other nuclear receptors including PPAR-gamma, PPAR-beta/delta, constitutive androstane receptor, pregnane X receptor, and estrogen receptor-alpha (Fenton et al., 2021).

Differences in PFAS toxicokinetic and toxicodynamic factors between animals and humans make it difficult to interpret the human relevancy of animal toxicity data (Fenton et al., 2021). For example, there are very large differences in PFAS elimination half-lives across species. In rats and mice, half-lives vary from hours to weeks, but in humans, estimated half-lives vary from days to several years (EFSA, 2020). In general, PFAS chemicals with a long perfluoroalkyl chain length have a longer elimination half-life than those with a short perfluoroalkyl chain length. For example, the half-lives in animals and humans estimated for PFOA (C8) are longer than those estimated for PFHpA (C7), PFHxA (C6), and PFBA (C4), and PFOS (C8) has longer estimated half-lives compared to PFBS (C4) (ATSDR, 2021; EFSA, 2020).

Health-based guidance values or TRVs for PFAS chemicals have been derived by many health agencies across the world, mainly for PFOA and PFOS and a few other well-studied PFAS chemicals (e.g., perfluorononanoic acid [PFNA], perfluorohexanesulfonic acid [PFHxS]). These values have been based on a variety of different health outcomes in animals and humans. For example, in 2020, EFSA established a tolerable weekly intake (TWI) of 4.4 ng/kg body weight per week for the sum of PFOA, PFNA, PFHxS, and PFOS based on reduced antibody response to vaccination in children (EFSA, 2020).

Additionally, several groups have proposed the use of the relative potency factor (RPF) approach as a tool for PFAS risk assessments covering multiple chemical substances. For example, the Dutch National Institute for Public Health and the Environment (RIVM) developed RPFs for 23 PFAS chemicals with PFOA as the index chemical (Zeilmaker et al., 2018; Bil et al., 2021). The RPFs were based on a database of liver endpoints from subchronic oral toxicity studies in male rats. Dose-response analysis was applied for three endpoints: absolute and relative liver weight and liver hypertrophy, but the final RPFs were based on relative liver weight. The RPFs in this study represent the ratio of the benchmark dose of the index compound (PFOA) and the benchmark dose of the other PFAS chemicals. Additionally, the RPFs of seven PFAAs that lacked any relevant data were estimated using a read-across approach. They were assumed to be between the derived RPFs of either perfluoroalkyl carboxylic acid (PFCA) or perfluoroalkyl sulfonic acid (PFSA) with a shorter or longer alkyl chain length. Several of the targeted PFAS chemicals for this report were included in the RPF analysis presented by Bil et al. (2021) as discussed in the sections below.

4.1.2. Existing TRVs and Hazard Identification

The literature searches conducted for this report identified existing chronic TRVs from authoritative sources for five of the targeted PFAS chemicals: PFBA, PFHxA, PFBS, DFE, and TFE. Dose-response data in mammalian animal models that can be used to derive a chronic TRV were identified for three of the targeted PFAS chemicals that lack an existing agency TRV: 6:2 FTOH, 8:2 FTOH, and PFHpA. No suitable dose-response data in mammals was identified for PFOSA.

4.1.2.1. Perfluorobutanoic Acid (PFBA) (CASRN 375-22-4)

Previous Human Health Assessments

Published agency noncancer TRVs are available for PFBA from EPA's Integrated Risk Information System (IRIS) (U.S. EPA, 2022) and the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) (2017) (Table 4) (see Supplemental File D for more details). Additionally, the German Environment Agency, Umwelt Bundesamt (UBA), recommended a POD and composite assessment factor to derive a safe drinking water limit for PFBA but did not report a final TRV for PFBA (UBA, 2023). Details on the critical effects and principal studies used in these assessments are described in the next section. ATDSR (2021) concluded there are insufficient data for derivation of MRLs for PFBA.

Table 4. Existing Agency Noncancer Toxicity Reference Values for PFBA.

Agency	Type of TRV	Critical Health Effects and Principal Study	TRV	Reference
U.S. EPA	Subchronic oral RfD	Developmental delays in mice (Das et al., 2008)	6×10^{-3} mg/kg/day	U.S. EPA (2022)
U.S. EPA	Chronic oral RfD	Hepatic and thyroid effects in rats (Butenhoff et al., 2012)	1×10^{-3} mg/kg/day	U.S. EPA (2022)
ANSES	Chronic oral iTV	Hepatic effects in rats (Butenhoff et al., 2012)	2.4×10^{-2} mg/kg/day	ANSES (2017)
UBA	POD and overall assessment factor for chronic oral reference value	Hepatic and thyroid effects in rats (Butenhoff et al., 2012)	(6 mg/kg/day ÷ 2,000 = 3×10^{-3} mg/kg/day)[a]	UBA (2023)

TRV = toxicity reference value; U.S. EPA = United States Environmental Protection Agency; RfD = reference dose; ANSES = French Agency for Food, Environmental and Occupational Health & Safety; iTV = indicative toxicity value = a toxicological benchmark that can be used for risk assessment that is less robust than the TRV and therefore has a lower confidence level; UBA = Umwelt Bundesamt (German Environment Agency); POD = point of departure.

[a]A TRV for PFBA was not explicitly reported in the UBA assessment but the POD (6 mg/kg/day) and overall assessment factor (2,000) that UBA recommended to derive a safe exposure level are reported here along with the resulting reference value that can be calculated by dividing those two values.

The EPA's IRIS and ANSES both derived chronic oral TRVs for PFBA based on a subchronic oral study in rats by Butenhoff et al. (2012) (described in the hazard identification section below). Both agencies used a no-observed-adverse-effect level (NOAEL) of 6 mg/kg/day as the basis for the POD and converted the POD to a human equivalent dose. The EPA (2022) derived a chronic oral RfD of 1×10^{-3} mg/kg/day for PFBA based on liver hypertrophy and decreased serum thyroxine (T4), and ANSES (2017) derived a chronic oral indicative toxicity value of 2.4×10^{-2} mg/kg/day for PFBA based on liver hypertrophy and functional signs related to liver and lipid metabolism. ANSES chose to establish an indicative toxicity value (iTV) for PFBA based on doubts about the choice of critical effect and its harmful nature in humans.

UBA also identified a NOAEL of 6 mg/kg/day based on hepatic and thyroid effects in Butenhoff et al. (2012) as a POD for PFBA and recommended an overall assessment factor of 2,000 to derive a safe drinking water limit for PFBA (UBA, 2023). Dividing those two values together results in a chronic oral TRV of 3×10^{-3} mg/kg/day.

EPA derived a subchronic oral RfD of 6×10^{-3} mg/kg/day for PFBA in the IRIS assessment, which was based on increased time to vaginal opening in neonatal female mice of the oral developmental study by Das et al. (2008). The EPA determined a BMDL of 3.8 mg/kg/day ammonium PFBA (3.52 mg/kg/day PFBA) for this effect, which was the basis for the POD (U.S. EPA, 2022).

Hazard Identification

The mammalian repeated dose animal toxicity database for PFBA includes several short-term studies in rats and mice, one subchronic study in rats, and one developmental study in mice (Foreman et al., 2009; Weatherly et al., 2021; Daugherty et al., 2023; Butenhoff et al., 2012; Das et al., 2008). No studies evaluating reproductive toxicity or chronic toxicity in animals were identified for PFBA. The toxicological profile of PFBA was recently reviewed and evaluated in an EPA IRIS assessment (U.S. EPA, 2022). Therefore, the health effects associated with PFBA are only briefly described here.

Exposure-related effects of PFBA in animals were mainly observed in the liver, thyroid, and offspring development (U.S. EPA, 2022). The longest exposure duration among the available studies is a 90-day oral study in male and female rats reported by Butenhoff et al. (2012). The same authors also report a 28-day study in rats.

Butenhoff et al. (2012) exposed male and female rats to ammonium PFBA by oral gavage at dose levels of 0–150 mg/kg/day for 28 days or 0–30 mg/kg/day for 90 days. Male rats were more sensitive to the effects of PFBA than female rats, most likely due to differences in toxicokinetic factors between the sexes (Butenhoff et al., 2012). The lowest-observed-adverse-effect level (LOAEL) was 30 mg/kg/day in male rats based on

increases in absolute and relative liver weight associated with hepatocellular hypertrophy, reductions in serum levels of free and total T4, and increases in the incidences of thyroid follicular hypertrophy/hyperplasia (Butenhoff et al., 2012). Additional exposure-related effects included changes in clinical chemistry indicative of liver injury (e.g., reductions in serum total cholesterol and total bilirubin and increases in serum liver enzyme levels). A NOAEL of 6 mg/kg/day was identified for both exposure durations (Butenhoff et al., 2012).

Other short-term exposure studies of PFBA in rodents observed similar effects as the Butenhoff study with some additional effects reported. Foreman et al. (2009) observed hepatocellular focal necrosis in the livers of wild-type mice orally exposed to PFBA for 28 days, and Weatherly et al. (2021) observed hepatocellular necrosis and epidermal necrosis in female mice dermally exposed to PFBA for 28 days. Additionally, Daugherty et al. (2023) reported that short-term oral exposure to PFBA in male rats before or during puberty resulted in increased serum testosterone concentrations and testicular testosterone production, and short-term oral exposure to PFBA before puberty resulted in increased testicular concentrations of 17β-estradiol, which is a type of estrogen.

One developmental study is available for PFBA. Das et al. (2008) exposed pregnant female mice to ammonium PFBA by oral gavage on gestation days 1–17 to doses of 0, 35, 175, or 350 mg/kg/day. Increases in absolute and relative liver weight were observed in the maternal animals exposed to doses ≥175 mg/kg/day and in their offspring on postnatal day 1. The most sensitive developmental effect was delayed eye opening at doses ≥35 mg/kg/day. Effects on litter resorption, pup survival, fetal absent testes, and delayed onset of puberty were seen at higher dose levels (Das et al., 2008). The LOAEL was 35 mg/kg/day and a NOAEL was not identified.

Human epidemiologic studies have evaluated the possible associations between PFBA exposure and many different health outcomes, and some significant associations have been observed for PFBA, including inverse associations with thyroid stimulating hormone (TSH) and birth weight (U.S. EPA, 2022). The EPA concluded that the available human evidence was indeterminate for effects that are consistently observed in animal studies (i.e., thyroid, liver, and developmental effects), and no human studies were selected for dose-response assessment (U.S. EPA, 2022). The EPA also concluded there are too few studies or a lack of consistent or coherent effects of PFBA exposure for other health outcomes that have been studied in humans (i.e., reproductive toxicity, immunosuppression, blood pressure, and renal function) to determine whether these outcomes might be potential health hazards of PFBA exposure (U.S. EPA, 2022). However, the general findings identify potential areas of future research.

Selected TRV

The chronic oral RfD for PFBA developed by the EPA (1×10^{-3} mg/kg/day) is selected to estimate risk in this report because it is the most conservative chronic TRV from an authoritative source.

4.1.2.2. Perfluorohexanoic Acid (PFHxA) (CASRN 307-24-4)

Previous Human Health Assessments

Published agency noncancer TRVs are available for PFHxA from IRIS (U.S. EPA, 2023b) and ANSES (ANSES, 2017) (Table 5) (see Supplemental File D for more details). Additionally, UBA recommended a POD to derive a safe drinking water limit for PFHxA, but did not report a final TRV (UBA, 2023). Details on the critical effects and principal studies used in these assessments are described in the next section. ATDSR (2021) concluded there are insufficient data for derivation of MRLs for PFHxA.

Table 5. Existing Agency Noncancer Toxicity Reference Values for PFHxA.

Agency	Type of TRV	Critical Health Effects and Principal Study	TRV	Reference
U.S. EPA	Subchronic and chronic oral RfD	Decreased body weight in offspring of rats (Loveless et al., 2009)	5×10^{-4} mg/kg/day	U.S. EPA (2023b)
ANSES	Chronic oral TRV	Kidney effects in female rats (Klaunig et al., 2015)	0.32 mg/kg/day	ANSES (2017)

TRV = toxicity reference value; U.S. EPA = United States Environmental Protection Agency; RfD = reference dose; ANSES = French Agency for Food, Environmental and Occupational Health & Safety.

The EPA's IRIS (2023) derived the same oral RfD of 5×10^{-4} mg/kg/day for subchronic and chronic exposure to PFHxA based on the critical effect of decreased postnatal body weight in male and female rats on postnatal day 0 in a one-generation oral study by Loveless et al. (2009). The EPA determined a BMDL of 10.62 mg/kg/day for this effect, which was the basis for the POD and converted to a human equivalent dose (U.S. EPA, 2023b).

ANSES (2017) derived a chronic oral TRV of 0.32 mg/kg/day for PFHxA based on the critical effect of papillary necrosis and tubular degeneration in the kidneys of female rats at the end of a 2-year oral study by Klaunig et al. (2015). ANSES used the NOAEL of 30 mg/kg/day as the basis for the POD and converted it to a human equivalent dose. Additionally, UBA recommended a no-observed-effect level (NOEL) of 15 mg/kg/day for low urine pH values in male rats from the 2-year study (Klaunig et al., 2015) as a POD to derive a safe drinking water limit for PFHxA (UBA, 2023).

Hazard Identification

The mammalian repeated dose animal toxicity database for PFHxA includes several short-term studies in rats and mice, two subchronic oral studies in rats and mice, one chronic oral study in rats, two oral developmental studies in rats and mice, and a one-generation oral reproductive study in rats (NTP, 2019a; Weatherly et al., 2023; Chengelis et al., 2009; Jiang et al., 2021; Loveless et al., 2009; Klaunig et al., 2015; Iwai and Hoberman, 2014). The toxicological profile of PFHxA was recently reviewed and evaluated in an EPA IRIS assessment (U.S. EPA, 2023b). Therefore, the health effects associated with PFHxA are only briefly described here.

Exposure-related effects of PFBA in animals were mainly observed in the liver, hematopoietic system, thyroid, and offspring development. Some effects were also observed in the kidney, male reproductive organ weights and hormones, sperm count, thymus weight, and spleen (U.S. EPA, 2023b).

Hepatotoxic effects of PFHxA included increases in relative liver weight and hepatocellular hypertrophy that were observed following short-term, subchronic, and chronic oral exposures (NTP, 2019a; Jiang et al., 2021; Chengelis et al., 2009; Loveless et al., 2009; Klaunig et al., 2015). Weatherly et al. (2023) also observed these effects in mice dermally exposed to PFHxA for 28 days. Short-term and subchronic oral studies also observed several changes in clinical chemistry indicative of liver damage (e.g., increases in alanine transaminase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], albumin to globulin ratio, and decreases in total protein and globulin) (NTP, 2019a; Chengelis et al., 2009; Loveless et al., 2009). Hepatocellular necrosis was observed only in female rats dosed with 200 mg/kg/day PFHxA for 2 years (Klaunig et al., 2015).

Consistent decreases in red blood cells, hematocrit, and hemoglobin were observed across exposure durations in male and female rats (U.S. EPA, 2023b). Changes in thyroid hormone levels in male rats were consistent with changes observed for other short-chain PFAS chemicals (i.e., decreased serum T4 and triiodothyronine [T3] with no significant changes in TSH) (U.S. EPA, 2023b). There were also exposure-related changes in thyroid histopathology and weight observed in male and female rats in one subchronic study (Loveless et al., 2009).

The kidney was affected by PFHxA exposure in some studies. Increases in absolute and relative kidney weights were observed in short-term, subchronic, and chronic oral studies (U.S. EPA, 2023b), and the incidence of chronic progressive nephropathy was increased for female rats following short-term exposure to 1,000 mg/kg/day (NTP, 2019a). Klaunig et al. (2015) reported null histopathological findings in the kidney for male rats but increases in papillary necrosis and tubular degeneration in the highest dose group (200 mg/kg/day) of female rats exposed to PFHxA for 2 years. Changes observed in blood biomarkers of

renal function were inconsistent across studies, and changes in urinalysis findings were difficult to interpret as adverse or nonadverse (U.S. EPA, 2023b).

Developmental and reproductive studies in rodents observed exposure-related decreases in fetal and postnatal offspring body weights (Iwai and Hoberman, 2014; Loveless et al., 2009). Biologically and/or statistically significant reductions in pup body weight were observed at oral doses ≥100 mg/kg/day (EPA, 2023), and the percent change from control was greatest for male and female pups on postnatal day 0 in a one-generation oral reproductive study in rats (Loveless et al., 2009). In that study, Loveless et al. (2009) exposed male and female rats to sodium PFHxA (0, 20, 100, or 500 mg/kg/day) for 70 days prior to mating, through gestation and lactation for a total of about four months. No exposure-related effects were observed on reproductive parameters. Besides effects on pup body weights, other developmental effects were seen at higher dose levels including increases in offspring mortality and delays in eye opening (Iwai and Hoberman, 2014; Loveless et al., 2009).

Human epidemiologic studies have evaluated the possible associations between PFHxA exposure and many different health outcomes, and some significant associations have been observed for PFHxA, including inverse associations with estimated glomerular filtration rate, T3, TSH, sperm motility, and testosterone (U.S. EPA, 2023b). The EPA concluded that the available human evidence was indeterminate for effects that are consistently observed in animal studies (i.e., liver, hematopoietic, thyroid, and developmental effects), and no human studies were selected for dose-response assessment (U.S. EPA, 2023b). The EPA also concluded there are too few studies for other health outcomes that have been analyzed in humans (i.e., reproductive, immune-related, and renal) to determine whether those outcomes might be potential health hazards of PFHxA exposure (U.S. EPA, 2023b). However, the general findings identify potential areas of future research.

Selected TRV

The chronic oral RfD for PFHxA developed by the EPA (5×10^{-4} mg/kg/day) is selected to estimate risk in this report because it is the most conservative chronic TRV from an authoritative source.

4.1.2.3. Perfluorobutane Sulfonic Acid (PFBS) (CASRN 375-73-5)

Previous Human Health Assessments

Published agency noncancer TRVs are available for PFBS from the EPA's IRIS (U.S. EPA, 2021), the California Office of Environmental Health and Hazard Assessment (OEHHA) (OEHHA, 2021), ANSES (ANSES, 2017), and UBA (UBA, 2023) (Table 6) (see Supplemental File D for more details). Details on the critical effects and principal studies used in these

assessments are described in the next section. ATDSR (2021) concluded there are insufficient data for derivation of MRLs for PFBS.

Table 6. Available Noncancer Toxicity Reference Values for PFBS.

Agency	Type of TRV	Critical Health Effects and Principal Study	TRV	Reference
U.S. EPA	Subchronic oral RfD	Decreased serum total T4 in newborn mice (Feng et al., 2017)	9×10^{-4} mg/kg/day	U.S. EPA (2021)
U.S. EPA	Chronic oral RfD	Decreased serum total T4 in newborn mice (Feng et al., 2017)	3×10^{-4} mg/kg/day	U.S. EPA (2021)
OEHHA	Chronic oral RfD	Decreased serum total T4 in GD 20 dams (Feng et al., 2017)	6×10^{-4} mg/kg/day	OEHHA (2021)
ANSES	Chronic oral TV	Renal tubular hyperplasia (Lieder et al., 2009b)	8×10^{-2} mg/kg/day	ANSES (2017)
UBA	Chronic oral TV	Reduced concentration of T3 and T4 in dams (at GD 20) and in the female offspring postnatally (Feng et al., 2017)	8.5×10^{-3} mg/kg/day	UBA (2023)

PFBS = perfluorobutanesulfonic acid; TRV = toxicity reference value; U.S. EPA = United States Environmental Protection Agency; RfD = reference dose; T4 = thyroxine; OEHHA = California Office of Environmental Health and Hazard Assessment; GD = gestation day; ANSES = French Agency for Food, Environmental and Occupational Health & Safety; TV = toxicity value; UBA = Umwelt Bundesamt (German Environment Agency); T3 = triiodothyronine.

The EPA, California OEHHA, and UBA all derived chronic oral toxicity values for PFBS based on decreases in thyroid hormone levels in offspring and/or pregnant dams in the developmental oral study in mice by Feng et al. (2017). The values are all within an order of magnitude of each other, and differences arise based on the selected POD (e.g., a derived BMDL or NOAEL) and composite uncertainty factor applied by each agency (see Supplemental File D for more details). The EPA used the same POD, a BMDL human equivalent dose of 0.095 mg/kg/day, for decreased serum total T4 in newborn mice, to derive subchronic and chronic RfDs for PFBS, but the EPA used a higher composite uncertainty factor for derivation of the chronic RfD (3×10^{-4} mg/kg/day), making it slightly lower than the subchronic RfD (9×10^{-4} mg/kg/day).

The ANSES assessment predates the publishing of the developmental study by Feng et al. (2017). Therefore, ANSES based a chronic oral TRV for PFBS on renal tubular hyperplasia observed in the parental animals of the reproductive study by Lieder et al. (2009b). ANSES derived a BMDL of 24 mg/kg/day for this effect and converted it to a human

equivalent dose to derive a chronic oral toxicity value of 8.5×10^{-3} mg/kg/day for PFBS (ANSES, 2017).

Hazard Identification

The mammalian repeated dose toxicity database for PFBS includes three short-term 28-day studies in rats, one subchronic study in rats, one subchronic-duration lipoprotein metabolism study in mice, three gestational exposure studies in mice and rats, and a two-generation reproductive toxicity study in rats (Daugherty et al., 2023; NTP, 2019b; Lieder et al., 2009a; Bijland et al., 2011; Feng et al., 2017; Lieder et al., 2009b; unpublished industry studies cited in U.S. EPA, 2021). No studies evaluating chronic toxicity (i.e., longer than 90 days of exposure) in animals were identified for PFBS; however, PFBS has been reported in serum of humans in the general population. The toxicological profile of PFBS was recently reviewed and evaluated in an EPA Provisional Peer-Reviewed Toxicity Values (PPRTV) assessment (U.S. EPA, 2021). Therefore, the health effects associated with PFBS are only briefly described here.

Exposure-related effects of PFBS in animals were mainly observed in thyroid hormone levels, the kidney, and offspring development. Some effects were also observed in the liver (U.S. EPA, 2021).

Thyroid effects of PFBS include similar patterns of decreases in total T3, total T4, and free T4 levels in PFBS-exposed adult male and female rats, pregnant mice, and gestationally exposed female mice offspring (NTP, 2019b; Feng et al., 2017). Significant effects occurred beginning at the lowest dose tested (62.6 mg/kg/day) in a 28-day oral study in rats by NTP (2019b) and at dose levels ≥200 mg/kg/day in a developmental oral study in mice (Feng et al., 2017). Low thyroid hormone levels can potentially lead to serious health consequences. Despite consistent changes in thyroid hormone levels, no exposure-related effects were observed on thyroid weights or histopathology (NTP, 2019b).

The kidney was affected by PFBS exposure in some animal studies. Increases in absolute and relative kidney weights and serum markers of renal injury were observed in a 28-day oral study in male and female rats, with females affected at the lowest dose tested (62.6 mg/kg/day) (NTP, 2019b). Additionally, the incidences of kidney mineralization, necrosis, and inflammatory changes were increased in female rats after subchronic exposure to 600 mg/kg/day PFBS, and papillary edema and hyperplasia were also increased in male rats exposed to 600 mg/kg/day (Lieder et al., 2009a). A two-generation reproductive study observed increases in minimal to mild microscopic findings in the medulla and papilla of the kidneys of male and female parental rats orally exposed to ≥300 mg/kg/day PFBS (Lieder et al., 2009b).

Developmental and reproductive studies of PFBS in rodents observed exposure-related decreases in offspring body weights (Feng et al., 2017; Lieder et al., 2009b) but no effects on offspring survival or fetal morphology (U.S. EPA, 2021). Developmental delays were reported for mice gestationally exposed to PFBS including delayed eye opening, delayed development of the female reproductive organs, and delayed and abnormal estrous cycling, which were concurrent with decreases in serum estradiol and increases in luteinizing hormone in pubertal female offspring (Feng et al., 2017). Luteinizing hormone is a key indicator of ovulation. No effects were observed on adult male and female fertility, pregnancy outcomes, and reproductive organ weights and histopathology in several studies (U.S. EPA, 2021).

Hepatic effects observed for PFBS included increases in absolute and/or relative liver weights after short-term and multigenerational exposure (NTP, 2019b; Lieder et al., 2009b). Studies did not consistently find effects of PFBS on liver histopathology (U.S. EPA, 2021). The exception is that two studies reported increases in hepatocellular hypertrophy in male rats (NTP, 2019b; Lieder et al., 2009b).

Human epidemiologic studies have evaluated the possible associations between PFBS exposure and many different health outcomes, including childhood adiposity (e.g., obesity), alteration of menstruation, reproductive hormones, semen parameters, kidney function, lung function, and lipid profile; however, significant positive associations with PFBS exposure have only been observed for a few outcomes (i.e., asthma, cardiovascular disease, hypertensive disorders of pregnancy, and serum cholesterol levels) (U.S. EPA, 2021). The EPA determined there was limited ability to draw conclusions about the potential health hazards of PFBS from the available epidemiology studies due to the small number of studies per outcome and poor sensitivity of the studies resulting from low exposure levels to PFBS; however, the general findings identify potential areas of future research.

Selected TRV

The chronic oral RfD for PFBS developed by the EPA (3×10^{-4} mg/kg/day) is selected to estimate risk in this report because it is the most conservative chronic TRV from an authoritative source.

4.1.2.4. 1,1-Difluoroethane (DFE) (CASRN 75-37-6)

Difluoroethane (DFE), also commonly referred to as HFC-152a, is a central nervous system depressant and volatile substance that can be inhaled recreationally. Several deaths have been reported after huffing, and abrupt cessation can induce withdrawal. See Supplemental File B for further discussion of prolonged or excessive use of DFE.

Previous Human Health Assessments

A chronic inhalation RfC for DFE is available from the EPA's IRIS (U.S. EPA, 1994). No other chronic TRVs were identified for DFE. The EPA used a NOAEL of 25,000 ppm from a chronic inhalation study in rats (McAlack and Schneider, 1982) as the POD and converted it to a human equivalent concentration of 12,051 mg/m^3 to derive a chronic RfC of 40 mg/m^3 for DFE, using a composite uncertainty factor of 300 (U.S. EPA, 1994).

Hazard Identification

The mammalian repeated dose animal toxicity database for DFE includes several short-term studies, one subchronic study, one developmental study, and one chronic exposure study. The only effects observed during a 2-week inhalation study of DFE in rats were anesthetic effects at 100,000 ppm (unpublished DuPont data reported in EPA IRIS, 1994), and the only adverse effect reported in a subchronic inhalation study was mild diffuse infiltration of cells in the lung, possibly indicating mild chronic irritation when rats were exposed to 100,000 ppm for 16 hours/day for 2 months (Lester and Greenberg, 1950 as cited in U.S. EPA, 1994).

There is limited information about the developmental toxicity of hydrofluorocarbons, but animal studies have shown this class of chemicals seems to have little potential to affect fetal development (Ema et al., 2010). The developmental toxicity and teratogenic potential of DFE was investigated in female rats exposed for 6 hours/day on days 6 through 15 of pregnancy to air containing 0, 5,000, or 50,000 ppm DFE (OECD SIDS, 2006). The authors found no adverse maternal, fetotoxic, or teratogenic effects of DFE. There is very limited information to assess the reproductive toxicity of hydrofluorocarbons as multiple-generation reproduction studies have not been performed (Ema et al., 2010).

One chronic exposure study is available for DFE (unpublished study by McAlack and Schneider, 1982 cited in EPA, 1994). In that study, male and female rats were exposed via inhalation to 0, 2,000, 10,000, or 25,000 ppm DFE for 6 hours/day, 5 days/week for 2 years. Hematology, clinical chemistry, and urinalysis were conducted at many different timepoints, and approximately 40 tissues were examined microscopically at interim and terminal sacrifices. No exposure-related adverse systemic effects were observed. Increases in the incidence of atrophy of the nasal olfactory epithelium were noted in some exposure groups at the end of the study compared to controls, but the EPA did not consider this effect to be adverse (U.S. EPA, 1994).

Selected TRV

The chronic inhalation RfC for DFE developed by EPA (40 mg/m^3) is selected to estimate risk in this report because it is the only chronic TRV available from an authoritative

source, and no new studies were identified that provide a lower POD for DFE. The selected values for acute TRVs are further described in Supplemental File B.

4.1.2.5. 1,1,1,2-Tetrafluoroethane (TFE) (CASRN 811-97-2)

Previous Human Health Assessments

A chronic inhalation RfC for TFE, also commonly referred to as HFC-134a, is available from the EPA's IRIS (U.S. EPA, 1995). No other chronic TRVs were identified. The EPA derived a benchmark concentration (BMC) for a 10% extra increase in Leydig cell hyperplasia for male rats in a chronic inhalation study (Collins et al., 1995) as the POD and converted it to a human equivalent concentration of 8,200 mg/m^3 to derive a chronic RfC of 80 mg/m^3 for TFE, using a composite uncertainty factor of 100 (U.S. EPA, 1995).

Hazard Identification

The mammalian repeated dose animal toxicity database for TFE includes several short-term, subchronic, developmental, and chronic studies. Short-term inhalation studies have noted increases in incidence of focal interstitial pneumonitis of the lungs of rats exposed to ≥50,000 ppm for 2 weeks and changes in liver, kidney, and testicular weights in rats exposed to 50,000 ppm for 28 days (6 hours/day, 5 days/week) (NRC, 2002). A subchronic inhalation study in rats produced no exposure-related microscopic changes in rats exposed to 0, 2,000, 10,000, or 50,000 ppm TFE for 90 days (6 hours/day, 5 days/week) (Collins et al., 1995).

There is limited information about the developmental toxicity of hydrofluorocarbons, but animal studies have shown this class of chemicals seems to have little potential to affect fetal development (Ema et al., 2010). A developmental study in rabbits showed reduced maternal weight gain in dams exposed to ≥10,000 ppm but no signs of developmental toxicity or teratogenicity (Collins et al., 1995). Two developmental studies in rats observed delayed fetal development, manifested as delayed skeletal ossification, when dams were exposed to ≥50,000 ppm on gestation days 6–15 for 6 hours/day (ECETOC, 2006). No multigeneration exposure study has been conducted for TFE, but fertility and peri- and postnatal exposure studies found no effects on reproductive performance or sexual development in rats exposed to concentrations up to 50,000 ppm (Alexander et al., 1996).

Two chronic inhalation studies are available for TFE with very few adverse effects reported. Collins et al. (1995) exposed male and female rats to 0, 2,500, 10,000, or 50,000 ppm TFE for 104 weeks (6 hours/day, 5 days/week). The only exposure-related effects found at the end of 2 years were in the testes, including increases in the incidences of testicular Leydig cell hyperplasia and benign Leydig cell adenoma in the male rats exposed to 50,000 ppm. Alexander et al. (1995) exposed rats and mice to

concentrations ≤50,000 ppm for 1 hour/day for 104–108 weeks and observed no effects on Leydig cells or any other adverse effects except for a dose-related increase in laryngitis in female rats. A NOEL of 10,000 ppm was reported (Alexander et al., 1995).

Selected TRV

The chronic inhalation RfC for TFE developed by the EPA (80 mg/m^3) is selected to estimate risk in this report because it is the only chronic TRV available from an authoritative source, and no new studies were identified that provide a lower POD for TFE. The selected values for acute TRVs are further described in Supplemental File B.

4.1.2.6. 6:2 Fluorotelomer Alcohol (6:2 FTOH) (CASRN 647-42-7)

Previous Human Health Assessments

No agency assessments reporting noncancer TRVs for 6:2 FTOH were identified.

Cahuas et al. performed a risk assessment of volatile PFAS chemicals released from paint into indoor air and used 6:2 FTOH as an example to estimate risk to consumers from typical use of paint containing this chemical (Cahuas et al. 2022; Cahuas, 2022). For hazard characterization, the authors chose a NOAEL of 5 mg/kg/day as the POD for 6:2 FTOH that was identified by the Danish Environmental Protection Agency (Danish EPA, 2015b). The POD is based on hematology and liver effects observed in a subchronic oral study by Serex et al. (2014) (described in the hazard identification section below). Cahuas (2022) derived a chronic reference dose of 5 × 10^{-3} mg/kg/day for 6:2 FTOH by applying a composite uncertainty factor of 1,000 to the POD.

Bil et al. (2021) estimated the relative potency of 23 PFAS chemicals for hepatic toxicity compared to PFOA as the index compound based on data for increases in liver weight and hepatocellular hypertrophy in subchronic studies of male rats. The RPF derived for 6:2 FTOH is 0.02, meaning that 6:2 FTOH was estimated to be 50 times less potent than PFOA for liver effects in male rats.

Because PFHxA is a metabolite of 6:2 FTOH, Rice et al. (2020) compared the toxicological profile of 6:2 FTOH to that of PFHxA and concluded it is significantly more concerning than PFHxA. The authors identify a NOEL of 1 mg/kg/day (from Mukerji et al., 2015) as the lowest systemic POD for 6:2 FTOH. Rice et al. concluded that oval cell hyperplasia and cyto-proliferative effects observed in the livers of both rats and mice raise the concern that 6:2 FTOH is likely to be a hepatocarcinogen in those species with possible relevance to humans.

Hazard Identification

6:2 FTOH is metabolically transformed through several steps to metabolites including PFBA, PFHxA PFHpA, perfluoropentanoate (PFPeA), x:3 fluorotelomer acids, and many conjugate metabolites, as demonstrated by oral and inhalation studies in rats and in vitro

studies in human hepatocytes (Rice et al., 2020). Several short-lived and highly reactive intermediate metabolites are formed, and some may have inherent toxicity; however, there are very few studies that have evaluated the toxicity of intermediate metabolites of fluorotelomer alcohols (Rand and Mabury, 2017). 5:3 fluorotelomer acid (5:3 acid) is a common metabolite for 6:2 FTOH in both rodents and humans, and it has the longest half-life of the evaluated metabolites in rats (Russell et al., 2015). Additionally, Nilsson et al. (2013) found that serum levels of 5:3 acid were elevated for months after human occupational exposure of ski wax technicians to 6:2 FTOH and other FTOHs in the air of their breathing zone, demonstrating its biopersistence in humans.

The mammalian repeated dose toxicity database for 6:2 FTOH includes short-term studies in rats by the oral or inhalation route, a combined 28-day oral repeated dose toxicity study with reproductive/developmental screening in rats, one subchronic oral study in rats, two oral reproductive (one-generation) studies in rats or mice, and three oral developmental studies in rats or mice (Table 7). No multigenerational reproductive studies or studies evaluating chronic toxicity in animals were identified for 6:2 FTOH. The critical effects listed in Table 7 are the adverse effects observed at the LOAEL of each study. Many other adverse effects were associated with higher doses in these studies.

Table 7. Available Repeated Dose Toxicity Studies for 6:2 FTOH.

Study Type and Species	Dose Levels and Exposure Paradigm	Critical Dose Levels and Effects Observed at LOAEL	Reference
4-week inhalation toxicity study in male and female rats	0, 1, 10, 100 ppm (6 hr/day, 5 days/week, whole body inhalation)	NOAEL = 10 ppm LOAEL = 100 ppm ↑ absolute and relative liver weight, serum bilirubin and ALT, basophilic striations within the inner dentin of incisor teeth ↓ motor activity (males)	Serex et al. (2012)
28-day oral toxicity study in male and female rats	0, 5, 25, 125 mg/kg/day (daily gavage)	NOAEL = 5 mg/kg/day LOAEL = 25 mg/kg/day ↑ relative liver weight, discolored incisors, mottled teeth (males)	Miyata (2007)
Combined repeated dose toxicity study with reproductive and developmental screening in rats	0, 25, 75, 225 mg/kg/day (14 days premating–LD 3) (daily gavage, 32–34 days for males, 39–44 days for females)	Parental NOAEL = 25 mg/kg/day Parental LOAEL = 75 mg/kg/day ↓ body weight, body weight gain Offspring NOAEL = 75 mg/kg/day Offspring LOAEL = 225 mg/kg/day ↓ number of pups born, postnatal survival, and pup weights	Kirkpatrick (2005)
90-day oral toxicity study in male and female rats	0, 5, 25, 125, 250 mg/kg/day (daily gavage)	NOAEL = 5 mg/kg/day LOAEL = 25 mg/kg/day	Serex et al. (2014)

Study Type and Species	Dose Levels and Exposure Paradigm	Critical Dose Levels and Effects Observed at LOAEL	Reference
		↑ TC and ALT (females), relative liver and kidney weights, oval cell hyperplasia in liver (females) ↓ RBC count, HGB, and HCT	
One-generation oral reproductive study in rats	0, 5, 25, 125, 250 mg/kg/day (70 days premating–LD 22) (daily gavage)	Parental/Offspring NOAEL = 5 mg/kg/day Parental/Offspring LOAEL = 25 mg/kg/day ↑ mortality in parental males, clinical signs, pup mortality ↓ parental body weight, food consumption, pup body weight	O'Connor et al. (2014)
One-generation oral reproductive study in mice	0, 1, 5, 25, 100 mg/kg/day (70 days premating–LD 21) (daily gavage, 107–109 days for parental males)	Parental NOAEL = 1 mg/kg/day Parental LOAEL = 5 mg/kg/day ↑ hepatocellular hypertrophy Offspring NOAEL = 25 mg/kg/day Offspring LOAEL = 100 mg/kg/day ↑ pup mortality, delayed maturation ↓ pup body weight	Mukerji et al. (2015)
Developmental oral study in rats	0, 5, 25, 125, 250 mg/kg/day (GD 6–20) (daily gavage)	Maternal and Offspring NOAEL = 25 mg/kg/day Maternal and Offspring LOAEL = 125 mg/kg/day ↓ maternal body weight and food consumption ↑ skeletal variations in fetuses	O'Connor et al. (2014)
Gestational exposure study in male mice	0, 5, 25, 125 mg/kg/day (GD 12.5–21.5) (daily gavage)	Offspring NOAEL = not determined Offspring LOAEL = 5 mg/kg/day ↑ delayed puberty, rate of sperm abnormality ↓ body weight, AGD, epididymal sperm count, sperm viability	Xia et al. (2023)
Gestational exposure study in mice	0, 5, 25, 125 mg/kg/day (GD 8.5–delivery) (daily gavage)	Offspring NOAEL = not determined Offspring LOAEL = 5 mg/kg/day ↑ anxiety-like behavior ↓ recognition index (learning memory)	Xia et al. (2024)

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; ALT = alanine transaminase; LD = lactation day; TC = total cholesterol; RBC = red blood cell; HGB = hemoglobin; HCT = hematocrit; GD = gestation day; AGD = anogenital distance.

Short-term oral and inhalation studies of 6:2 FTOH observed similar exposure-related effects in the teeth (e.g., discolored incisors and mottled teeth) and increases in liver weight. In male rats, decreased motor activity was observed during inhalation and oral

exposure periods (Serex et al., 2012; Miyata, 2007). Hepatocellular hypertrophy (oral exposure only) and clinical chemistry changes indicative of liver injury were also observed (Serex et al., 2012; Miyata, 2007; Kirkpatrick, 2005). Other exposure-related effects in short-term studies included increases in kidney weights along with tubular degeneration and dilatation in the kidney, and effects on the stomach and intestinal tracts, adrenal cortex, sternal bone marrow, pancreas, lymph nodes, spleen, and thymus (Miyata, 2007; Kirkpatrick, 2005). Deaths attributed to kidney, adrenal cortex, or bone marrow damage occurred in several rats dosed with 225 mg/kg/day (Kirkpatrick, 2005).

Subchronic oral exposure to 6:2 FTOH produced similar exposure-related effects in rats as the short-term studies (Serex et al., 2014). Signs of anemia were seen in both sexes, but in males at a lower dose level. Increases in relative liver and kidney weight correlated with exposure-related microscopic changes in both organs at higher doses including increased incidences of several lesions in the liver (e.g., oval cell hyperplasia, hepatocellular necrosis, hepatocellular hypertrophy, periportal inflammation, biliary hyperplasia). Females were slightly more sensitive to the hepatic effects of 6:2 FTOH than were males. Deaths attributed to kidney damage were reported for one rat in the 125 mg/kg/day group and several rats in the 250 mg/kg/day group. Exposure-related changes were also observed in the nasal cavity, teeth, thyroid, thymus, spleen, and pancreas at dose levels higher than those causing liver effects (Serex et al., 2014; Rice et al., 2020).

In one-generation reproductive studies in rats and mice, adverse effects of 6:2 FTOH on development were found, but effects on pups mainly occurred at dose levels that also produced parental toxicity (≥100 mg/kg/day). There were no exposure-related effects on reproductive performance (e.g., mating and fertility indices) (O'Connor et al., 2014; Mukerji et al., 2015). The one-generation reproductive study in mice noted increases in hepatocellular hypertrophy in parental males and females at ≥5 mg/kg/day (Mukerji et al., 2015). Several other lesions in the liver were increased in the highest dose group of parental males and females (e.g., necrosis, cystic degeneration, and oval cell hyperplasia). Microscopic alterations of incisor teeth were also observed in parental animals at high doses in the reproductive studies (O'Connor et al., 2014; Mukerjii et al., 2015). The developmental study in rats noted an increase in the incidence of fetal skeletal variations (e.g., incomplete ossification) at dose levels causing maternal toxicity (≥125 mg/kg/day) (O'Connor et al., 2014).

Two gestational exposure studies in mice evaluated very specific, sensitive endpoints in adult or adolescent offspring following in utero exposure to 6:2 FTOH (Xia et al., 2023; Xia et al., 2024). The authors observed significant changes in several endpoints in the lowest dose group (5 mg/kg/day) of both studies. Xia et al. (2023) evaluated male offspring only and reported a delay in the timing of male puberty and decreases in male body weight

and anogenital distance on postnatal days 22 and 50. Relative testis weight was decreased only in the highest dose group, but significant effects on sperm morphology, viability, and count were found in all dose groups. Xia et al. (2024) evaluated offspring in open field and new object recognition tests on postnatal day 22 and found increases in anxiety-like behavior and a decrease in object recognition when both sexes were analyzed together. Only one timepoint was evaluated for each test, and no clear dose-response trend was observed for any endpoint measured. Both studies in mice evaluated small samples sizes (n = 6–8), and the authors did not report whether the litter was the statistical unit of analysis, which is an important consideration when offspring are exposed as a litter through the maternal animal only. This limitation makes it difficult to interpret the results from these two studies.

No human epidemiologic studies were identified for 6:2 FTOH.

In summary, the liver and kidney were the primary target organs of 6:2 FTOH in rats and mice, as evidenced by increases in liver and kidney weights, elevations in clinical chemistry parameters indicative of liver damage, and histological changes in those organs. Hepatocellular hypertrophy was the most sensitive effect observed in the liver, but a variety of more severe liver lesions were seen at higher dose levels. 6:2 FTOH also had effects on the teeth in several studies, consistent with fluoride exposure from the release of fluoride during metabolism. Exposure-related signs of anemia were also commonly observed. Mortality observed at relatively high oral doses of 6:2 FTOH was most often attributed to severe kidney damage. Reproductive and developmental studies found exposure-related effects on pup viability, growth, and maturation, and increases in skeletal variations evaluated in fetuses. Many other organs had changes at dose levels higher than those causing liver toxicity. There is only one inhalation study identified for 6:2 FTOH and the exposure-related effects were similar to effects seen in oral studies. Mice were generally more sensitive to the effects of 6:2 FTOH than rats. Two gestational exposure studies in mice observed effects on the developing male reproductive system and neurodevelopment at dose levels lower than those causing effects on pup survival and body weight in other developmental and reproductive studies.

Selected Critical Effects and Approaches for TRV Derivation

The lowest effect level identified for 6:2 FTOH is from the one-generation reproductive study in mice (Mukerji et al., 2015), which provides a NOAEL of 1 mg/kg/day (LOAEL of 5 mg/kg/day) for hepatocellular hypertrophy observed in parental males and females. Additionally, two gestational exposure studies in mice (Xia et al., 2023; Xia et al., 2024) both provide a relatively low LOAEL of 5 mg/kg/day for sensitive effects on the male reproductive system and neurodevelopment (NOAEL not determined). These three studies and the critical effects they identified are selected for derivation of candidate

PODs and TRVs for screening-level risk assessment of 6:2 FTOH in this report (see Section 4.1.3).

Additionally, the RfD (5×10^{-3} mg/kg/day) derived by Cahuas et al. (2022), the POD (NOEL of 1 mg/kg/day) identified by Rice et al. (2020), and the RPF (0.02) derived by Bil et al. (2021) are used to derive candidate TRVs for 6:2 FTOH in this report (see Section 4.1.3). For the RPF approach, the most recent agency TRV for PFOA (the EPA chronic RfD of 3×10^{-8} mg/kg/day; U.S. EPA, 2024b) was divided by the 6:2 FTOH RPF for hepatic effects (0.02) to derive a candidate TRV. Finally, because this chemical has limited toxicity data (i.e., no chronic data), a direct read-across approach was used as an alternative method to identify a TRV for 6:2 FTOH. PFHxA was the source chemical chosen because it has chronic toxicity data, and it is a metabolite of 6:2 FTOH (Russell et al., 2015). The TRV selected for read-across to 6:2 FTOH is the EPA chronic RfD for PFHxA (5×10^{-4} mg/kg/day; U.S. EPA, 2023b).

4.1.2.7. 8:2 Fluorotelomer Alcohol (8:2 FTOH) (CASRN 678-39-7)

Previous Human Health Assessments

No agency assessments reporting noncancer TRVs for 8:2 FTOH were identified.

Himmelstein et al. (2012) conducted an inhalation toxicokinetic study in rats for 8:2 FTOH and used the data to estimate human equivalent air concentrations based on oral doses from a subchronic study in rats. They derived a BMDL10 of 3.69 mg/kg/day for the critical effect of liver necrosis in male rats from a subchronic oral study (Ladics et al., 2008), adjusted it for allometric scaling (animal to human), and divided it by an uncertainty factor of 2 (for extrapolation from subchronic to chronic exposure) resulting in a human equivalent oral dose of 0.52 mg/kg. This dose was converted to human equivalent concentrations in air (1.8 or 3.7 mg/m^3, based on alveolar ventilation of 20 or 10 m^3/day, respectively, for a 70 kg human) for comparison to various exposure scenarios. The authors assumed 100% absorption via inhalation and used oral absorption factors reported by Fasano et al. (2006) for 8:2 FTOH.

Sha et al. (2018) used read-across from PFOA to estimate a safe exposure level for 8:2 FTOH in their risk assessment of indoor air exposure. The authors state, "Since 8:2 FTOH is a precursor to PFOA and little information was found about reference values of FTOHs in air (…), the provisional tolerable daily intake for PFOA (1.5×10^6 pg/kg body weight/day) suggested by EFSA (2008) was used as the RfD for 8:2 FTOH."

Bil et al. (2021) estimated the relative potency of 23 PFAS chemicals for hepatic toxicity compared to PFOA as the index compound based on data for increases in liver weight and hepatocellular hypertrophy in subchronic studies of male rats. The RPF derived for 8:2 FTOH is 0.04, meaning that 8:2 FTOH was estimated to be 25 times less potent than PFOA for liver effects in male rats.

Hazard Identification

8:2 FTOH is metabolically transformed through several steps to PFOA and to a lesser extent to PFNA, PFHpA, and PFHxA, as demonstrated by oral studies in rats and mice and in vitro studies in human hepatocytes and liver microsomes (EFSA, 2020). Several short-lived intermediate metabolites are formed, and some may have inherent toxicity. Himmelstein et al. (2012) found that the most abundant metabolites in the plasma of rats exposed to 8:2 FTOH via inhalation were 8:2 fluorotelomer carboxylic acid (FTCA), 7:3 FTCA, and PFOA. This observation is consistent with the metabolite profile observed by Fasano et al. (2009) in the plasma of rats exposed via oral gavage, who also quantified several other metabolites in the urine, feces, liver, and kidney of rats orally exposed. Nilsson et al. (2013) found that 7:3 FTCA was a particularly biopersistent metabolite, along with 5:3 acid (a common metabolite of 6:2 FTOH), in ski wax technicians occupationally exposed to high concentrations of FTOHs in the air of their breathing zone. Those two metabolites were detected in serum samples collected throughout the summer months when the subjects were not working with ski wax (Nilsson et al., 2013). Little is known about the toxicity of these metabolites and the other intermediate metabolites of fluorotelomer alcohols (Rand and Mabury, 2017).

The mammalian repeated dose toxicity database for 8:2 FTOH includes a short-term oral immunotoxicity study in mice, a subchronic oral study in rats, and two developmental oral studies in rats or mice (Table 8). No multigenerational reproductive studies or studies evaluating chronic toxicity in animals were identified for 8:2 FTOH. The critical effects listed in Table 8 are the adverse effects observed at the LOAEL of each study. Many other adverse effects were associated with higher doses in these studies.

Table 8. Available Repeated Dose Toxicity Studies for 8:2 FTOH.

Study Type and Species	Dose Levels and Exposure Paradigm	Critical Dose Levels and Effects Observed at LOAEL	Reference
28-day oral immunotoxicity study in male mice	0, 10, 30, 100 mg/kg/day (daily gavage)	NOAEL = not determined LOAEL = 10 mg/kg/day ↑ absolute and relative liver weight, liver vacuolation, absolute thymus weight	Wang et al. (2019)
90-day oral toxicity study in male and female rats	0, 1, 5, 25, 125, mg/kg/day (daily gavage)	NOAEL = not determined LOAEL = 1 mg/kg/day ↑ colloid alteration in thyroid	Ladics et al. (2008)
Developmental oral study in rats	0, 50, 200, 500 mg/kg/day (GD 6–20) (daily gavage)	Maternal NOAEL = 200 mg/kg/day Maternal LOAEL = 500 mg/kg/day ↑ mortality, clinical signs of toxicity ↓ body weight and body weight gain Offspring NOAEL = 50 mg/kg/day	Mylchreest et al. (2005)

Study Type and Species	Dose Levels and Exposure Paradigm	Critical Dose Levels and Effects Observed at LOAEL	Reference
		Offspring LOAEL = 200 mg/kg/day ↑ incomplete skull ossification in fetuses	
Developmental study in mice	0, 30 mg/kg/day (single gavage dose GD 8)	Maternal and offspring NOAEL = not determined Maternal and offspring LOAEL = 30 mg/kg/day ↑ relative liver weight in maternal and neonatal animals, neonatal mortality, neural tube defects	Henderson and Smith (2007)

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; GD = gestation day.

The liver was a common target organ in short-term and subchronic studies of 8:2 FTOH, and the kidney, thyroid, and teeth were also affected by 8:2 FTOH following subchronic exposure. Wang et al. (2019) observed increases in absolute and relative liver weight and changes in liver histopathology (i.e., vacuolation) in all dose groups of male mice exposed via oral gavage to ≥10 mg/kg/day 8:2 FTOH for 28 days. Other histopathological effects in the liver were also observed in the highest dose groups of that study. Increases in absolute thymus weight were also observed in all dose groups of males exposed for 28 days, but no histological changes were observed in the thymus in that study or other studies (Wang et al., 2019).

Subchronic (90-day) oral exposure to 8:2 FTOH in rats produced increases in liver weight accompanied by focal liver necrosis in both sexes at ≥25 mg/kg/day (Ladics et al., 2008). Increases in the incidence of altered colloid in the thyroid were also observed in male rats from all dose groups (≥1 mg/kg/day) (Ladics et al., 2008). The kidney and teeth were additional target organs identified from subchronic oral exposure. Increases in the incidence of renal tubular hypertrophy were observed in male rats (≥25 mg/kg/day) and chronic progressive nephrotoxicity in female rats (125 mg/kg/day) (Ladics et al., 2008). Degeneration and/or disorganization of enamel organ ameloblast cells was observed in the incisors of male rats in the 125 mg/kg/day dose group, and minimal changes in clinical chemistry parameters indicative of liver injury were mainly observed at the highest dose level in the subchronic study (Ladics et al., 2008). The authors considered the NOAEL to be 5 mg/kg/day (LOAEL of 25 mg/kg/day) based on increases in liver necrosis and renal tubular hypertrophy in male rats; however, significant changes were observed in the thyroids of males from all dose groups. Given that other structurally similar PFAS chemicals have been associated with significant effects on the thyroid and thyroid hormone levels (as described for several of the targeted PFAS chemicals within this assessment), a LOAEL of 1 mg/kg/day is identified for this study in this report. The EPA

also identified a LOAEL of 1 mg/kg/day for this study (reported on the EPA CompTox Chemicals Dashboard).

Developmental toxicity was observed in both rats and mice exposed to relatively high doses of 8:2 FTOH via oral gavage. A standard oral developmental study in rats observed increases in the incidence of incomplete skull bone ossification in fetuses exposed to ≥200 mg/kg/day, but no other significant developmental effects (Mylchreest et al., 2005). Henderson and Smith (2007) exposed pregnant mice to a single oral dose of 30 mg/kg of 8:2 FTOH on gestation day 8 and increases in relative liver weight were observed for maternal animals through lactation day 15 and in pups on postnatal day 15. Neonatal body weights were unaffected by exposure in that study, but postnatal viability was decreased and the incidence of neural tube defects increased in neonates of the 8:2 FTOH exposure group (Henderson and Smith, 2007). The authors used a cross-fostering design and demonstrated that measurable amounts of PFOA and PFNA are transferred to the neonate during in utero or lactational exposure to 8:2 FTOH (Henderson and Smith, 2007).

Because of the paucity of toxicity data available for 8:2 FTOH, information from alternative animal models was also considered during hazard assessment. Two studies in zebrafish were identified that demonstrated effects of 8:2 FTOH on endocrine disruption, reproduction, and offspring mortality (Liu et al., 2010; Britton et al., 2024). Rosenmai et al. (2013) also examined the potential for endocrine disruption and found that 8:2 FTOH led to an increase in estrone and a decrease in progesterone, androstenedione, dehydroepiandrosterone, and testosterone in an H295R steroidogenesis assay, which is an in vitro screening study that can indicate the potential for endocrine disruption in humans.

One human epidemiologic study was identified for 8:2 FTOH. Jin et al. (2020) studied the associations between PFAS concentrations in human breast milk with postnatal infant growth and found that infants exposed to higher levels of 8:2 FTOH were correlated with decreased weight gain rate, although the statistical significance of this association was not reported.

In summary, the liver and kidney were the primary target organs of 8:2 FTOH in rats in mice, and changes in the thyroid were also detected in male rats only. 8:2 FTOH also had effects on teeth, consistent with fluoride exposure from the release of free fluoride during metabolism, and on offspring development as evidenced by increases in neonatal mortality and the incidences of incomplete skull ossification and neural tube defects. One study in humans found an association between 8:2 FTOH exposure and decreased weight gain in infants. Alternative models suggest 8:2 FTOH may have endocrine disrupting effects.

Selected Critical Effects and Approaches for TRV Derivation

The lowest effect level for 8:2 FTOH is from the 90-day oral study in rats (Ladics et al., 2008), which provides a LOAEL of 1 mg/kg/day for colloid alterations in the thyroids of male rats (NOAEL not determined). The 28-day study in mice (Wang et al., 2019) also provides a relatively low LOAEL of 10 mg/kg/day for increased absolute and relative liver weight in male mice (NOAEL not determined). These two studies and the critical effects they identified are selected for derivation of candidate PODs and TRVs for screening-level risk assessment of 8:2 FTOH in this report (see Section 4.1.3).

Additionally, the POD (BMDL10 human equivalent dose [HED] of 1.04 mg/kg/day) and human oral dose (0.52 mg/kg/day) derived by Himmelstein et al. (2012) and the RPF (0.04) derived by Bil et al. (2021) are used to derive candidate TRVs for 8:2 FTOH in this report (see Section 4.1.3). For the RPF approach, the most recent agency TRV for PFOA (the EPA chronic RfD of 3×10^{-8} mg/kg/day; U.S. EPA, 2024b) was divided by the 8:2 FTOH RPF for hepatic effects (0.04) to derive a candidate TRV for 8:2 FTOH. Finally, because this chemical has limited toxicity data (i.e., no chronic data), a direct read-across approach was used as an alternative method to identify a TRV for 8:2 FTOH. PFOA was the source chemical chosen because it has chronic toxicity data, and it is a metabolite of 8:2 FTOH (Himmelstein et al., 2012). The TRV selected for read-across to 8:2 FTOH is the EPA chronic RfD for PFOA (3×10^{-8} mg/kg/day; U.S. EPA, 2024b).

4.1.2.8. Perfluoroheptanoic Acid (PFHpA) (CASRN 375-85-9)

Previous Human Health Assessments

Most of the prior assessments identified for PFHpA used a read-across approach from PFOA or PFOS to determine a TRV for PFHpA (Swedish EPA, 2012; MassDEP, 2018; TCEQ, 2023; Massarsky et al., 2024; De la Torre et al., 2019). The only exception is an assessment from UBA, which recommended a POD and overall assessment factor to derive a safe drinking water limit for PFHpA based on data for the chemical itself, but did not report a final TRV (UBA, 2023) (Table 9). Details on the critical effect and the principal study used in this assessment are described in the next section. ATDSR (2021) concluded there are insufficient data for derivation of oral and inhalation MRLs for PFHpA.

Table 9. Available Noncancer Toxicity Reference Values for PFHpA.

Agency	Type of TRV	Critical Health Effects and Principal Study	TRV	Reference
UBA	POD and overall assessment factor for chronic oral reference value	Hepatocellular necrosis (Anonymous, 2017 cited in ECHA, 2020)	(6.63 mg/kg/day ÷ 50 = 0.1326 mg/kg/day)[a]	UBA (2023)

TRV = toxicity reference value; UBA = Umwelt Bundesamt (German Environment Agency); POD = point of departure.
[a]A TRV for PFHpA was not explicitly reported in the UBA assessment but the POD (BMDL5 = 6.63 mg/kg/day) and overall assessment factor (50) that UBA recommended to derive a safe exposure level are reported here along with the resulting reference value that can be calculated by dividing those two values.

UBA derived a BMDL5 (lower confidence interval of the benchmark dose for a 5% effective level) for hepatocellular necrosis in male rats from an unpublished study of PFHpA reported in ECHA (2020) and recommended that value as the starting point to derive a safe drinking water limit for PFHpA along with an overall assessment factor of 50. A final TRV is not reported in the assessment, but dividing the recommended POD by the overall assessment factor provides a chronic oral TRV of 0.1326 mg/kg/day for PFHpA.

In 2012, the Swedish Environmental Protection Agency (Swedish EPA) carried out a risk assessment of 23 PFAS chemicals, which included PFHpA. Hepatotoxicity and reproductive toxicity were identified as the priority endpoints and TRVs were derived for both. For PFAS chemicals lacking internal dose measurements or toxicity data for those endpoints, the agency used a read-across approach from the closest most potent congener for the respective endpoint. PFOA was used as the surrogate for PFHpA for both endpoints. The derived-no-effect-level (DNEL) for hepatotoxicity for PFHpA was 142 ng/mL serum (based on an external dose NOAEL of 0.06 mg/kg/day for PFOA); the DNEL for PFHpA for reproductive toxicity was 628 ng/mL (Swedish EPA, 2012).

The Massachusetts Department of Environmental Protection (MassDEP) (2018) applied the 2016 EPA chronic oral RfDs for PFOA and PFOS (both 2×10^{-5} mg/kg/day) to PFHpA, and the Texas Commission on Environmental Quality (TCEQ) (2023) applied the chronic oral RfD it derived for PFOS (2.3×10^{-5} mg/kg/day) to PFHpA, given that they have the same carbon chain length. Other U.S. state agencies have used read-across approaches for PFHpA in the past, but recent assessments were not found. De la Torre et al. (2019) used the RfD determined by MassDEP for PFHpA in their risk assessment of PFAS exposure from house dust in European countries, and Massarsky et al. (2024) used the RfD determined by TCEQ for PFHpA in their risk assessment of PFAS exposure from leave-in dental products.

PFHpA has a chemical structure very similar to PFOA, with the only difference being 1 fewer fluorinated carbon in the chain. In general, PFCAs with shorter chain lengths than PFOA are generally considered less bioaccumulative and, therefore, less potent than PFOA for several health endpoints. For example, Bil et al. (2021) used read-across methodology to estimate that the potency of PFHpA for hepatic toxicity is between the value derived for PFHxA (0.01) and PFOA (1). In this study, a RPF of 0.01 is equivalent to 100 times less potent than PFOA for hepatic effects in male rats. Therefore, the read-across outcome is interpreted as PFHpA is approximately 100 times less potent to equally as potent as PFOA for inducing liver effects in male rats. However, a recent study

in adolescents measured liver-to-plasma ratios of seven PFAS chemicals and reported that the highest ratios were found for PFHpA, which was 26 times higher than for PFOA (Baumert et al., 2023). These results come from only one study in 64 adolescents with high variability observed, but it raises the concern that PFHpA might have similar or more potential for accumulation in target organs compared to PFOA. Differences in elimination half-lives may affect relative toxic potency of PFHpA to PFOA, but these data are very limited for PFHpA. One study estimated that the half-life of PFHpA in humans is around 1 year, while the half-life of PFOA measured in several human studies ranges from 1.2 to 8.5 years (EFSA, 2020).

Hazard Identification

The mammalian repeated dose toxicity database for PFHpA includes three short-term studies in rats or mice, one gestational exposure study in male mice, and an unpublished 90-day oral toxicity study with reproductive and developmental toxicity screening in mice (Table 10). No multigenerational reproductive studies or studies evaluating chronic toxicity in animals were identified for PFHpA. The critical effects listed in Table 10 are the adverse effects observed at the LOAEL of each study. Several other adverse effects were associated with higher doses in these studies.

Table 10. Available Repeated Dose Toxicity Studies for PFHpA.

Study Type and Species	Dose Levels and Exposure Paradigm	Critical Dose Levels and Effects Observed at LOAEL	Reference
2-week dermal toxicity study in male and female rats	0, 250, 1,000 mg/kg/day (topical application, occlusive)	NOAEL = not determined LOAEL = 250 mg/kg/day ↑ liver weight, hepatocellular hypertrophy, skin ulceration, epidermal hyperplasia and parakeratosis, hepatocellular necrosis (males), renal tubular degeneration/dilation (females) ↓ prostate weight	Han et al. (2020)
28-day dermal toxicity study in female mice	0, 31.25, 62.5, 125 mg/kg/day (topical application, non-occlusive)	NOAEL = not determined LOAEL = 31.25 mg/kg/day ↑ hepatocellular hypertrophy	Weatherly et al. (2023)
3-week oral toxicity study in male rats	0, 10, 50, 100 mg/kg/day (daily gavage)	NOAEL = 50 mg/kg/day LOAEL = 100 mg/kg/day ↑ Leydig cell hyperplasia, serum levels of testosterone, luteinizing hormone, follicle-stimulating hormone ↓ absolute and relative testis weight, absolute epididymis weight, sperm production	Li et al. (2021)

Study Type and Species	Dose Levels and Exposure Paradigm	Critical Dose Levels and Effects Observed at LOAEL	Reference
Gestational exposure study in male mice	0, 0.0015, 0.015, 0.15 mg/kg/day (GD 1–16) (daily gavage)	NOAEL = not determined LOAEL = 0.0015 mg/kg/day ↑ progressive sperm head area ↓ sperm count, sperm concentration, total cell count in epididymis	Zhou et al. (2023)
Combined 90-day oral toxicity study with reproductive and developmental screening in male and female mice	0, 0.5, 10, 50 mg/kg/day (daily gavage) (109–113 days males, 90 days premating–LD 20 females)	Parental NOAEL = not determined Parental LOAEL = 0.5 mg/kg/day ↑ hepatocellular hypertrophy and necrosis Offspring NOAEL = not determined Offspring LOAEL = 0.5 mg/kg/day ↑ hepatocellular hypertrophy Developmental NOAEL = 0.5 mg/kg/day Developmental LOAEL = 10 mg/kg/day ↑ skeletal malformations	Anonymous (2017) cited in ECHA (2020)

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; GD = gestation day; LD = lactation day.

Short-term dermal application of PFHpA produced several adverse local and systemic effects in male and female rats and mice. Han et al. (2020) dermally exposed rats with PFHpA for 2 weeks and observed exposure-related effects in skin, liver, and kidney histopathology at the lowest dose tested and several other effects at the highest dose tested (e.g., renal tubular necrosis, thyroid follicular cell hypertrophy, lymphoid atrophy, germ cell degeneration in the testes, oligospermia in the epididymis). Similarly, Weatherly et al. (2023) observed adverse effects in the liver and skin of female mice dermally exposed to PFHpA for 28 days including increases in relative liver weight and centrilobular hepatocellular hypertrophy, increases in absolute kidney weight, decreases in serum blood urea nitrogen, and histopathological effects in the skin (e.g., epidermal hyperplasia and hyperkeratosis).

Li et al. (2021) exposed 35-day-old male rats to PFHpA by oral gavage for 3 weeks and observed reductions in testis and epididymis weights and sperm production, and increases in serum levels of testosterone, luteinizing hormone, and follicle-stimulating hormone and the incidence of Leydig cell hyperplasia only at the highest dose level. Non-reproductive organs were not evaluated in this study.

Zhou et al. (2023) exposed pregnant mice to very low dose levels of PFHpA (0.0015–0.15 mg/kg/day) and observed several exposure-related effects in male offspring in

adulthood including dose-related reductions in sperm count, sperm concentration, and total cell count in epididymis along with increases in progressive sperm head area all observed at the lowest dose level. Exposure-related changes in the testes were described qualitatively only and occurred in the mid- and high-dose groups. General developmental effects, such as litter size, birth weight, growth, milestones, and survival, are not reported in this study (and assumed to be not evaluated). The offspring were not mated, so it is unknown whether the changes in sperm parameters affected their fertility. Additionally, there is uncertainty in the doses that reached the offspring because PFHpA levels in the blood were not measured. The LOAEL for male reproductive endpoints was 0.0015 mg/kg/day based on changes in sperm count and concentration coherent with exposure-related changes in the testes at higher dose levels. A NOAEL was not determined for those effects.

The longest duration repeated dose study identified for PFHpA is an unpublished combined 90-day oral toxicity study with reproductive/developmental screening in mice (Anonymous, 2017 as cited in ECHA, 2020). The full study report was not located, but a description of the study, along with some quantitative results, is included in an opinion published by the ECHA Committee for Risk Assessment (ECHA, 2020). According to that source, male and female mice were exposed to PFHpA by oral gavage for 90 days prior to mating. Males were further exposed during mating, and females during mating, gestation, and lactation. There were no reproductive or behavioral effects on the P_0 animals. Liver toxicity was observed in parental and offspring exposure groups, demonstrated by increases in absolute and relative weights (≥10 mg/kg/day) and increases in centrilobular hepatocellular hypertrophy and hepatocellular necrosis even in the lowest dose group (0.5 mg/kg/day). Changes in liver-related clinical chemistry parameters were seen for initial parental (P_0) males, and serum T4 levels were decreased in the mid- and high-dose P_0 males (P_0 females were not analyzed). Slight effects on serum T4 levels were also seen in the first filial generation (F_1) males and females, but in opposite directions. In the F_1 offspring, PFHpA caused liver toxicity evidenced by increases in hepatocellular hypertrophy at all dose levels and necrosis at the mid- and high-dose levels. Reductions in postnatal survival and pup body weights were observed for the high-dose group only. However, dose-related increases in the incidences of malformations of the skeleton (i.e., missing digits, mal-rotated forelimbs, small stature) were observed at ≥10 mg/kg/day. Additionally, a delay in the onset of puberty was observed only for female offspring in the high-dose group, but there were no effects observed on mammary gland development. The parental and offspring LOAEL was 0.5 mg/kg/day based on liver toxicity and the developmental LOAEL was 10 mg/kg/day based on skeletal malformations in the absence of general toxicity in the dams (except for liver toxicity).

Because of the paucity of toxicity data available for PFHpA, information from alternative animal models was also considered during hazard assessment. Several studies in

zebrafish were identified. Most studies in zebrafish did not find significant effects of PFHpA (Dasgupta et al., 2020; Truong et al., 2022; Britton et al., 2024); however, one study found that PFHpA caused abnormal behavior in zebrafish following exposure during development (Rericha et al., 2021).

Human epidemiologic studies have evaluated the possible associations between PFHpA exposure and many different health outcomes. ATSDR (2021) concluded that there are too few studies for some outcomes or inconsistent results across studies for other outcomes to determine whether PFHpA was associated with the studied outcomes. The outcomes included those related to hepatic, renal, immune, developmental, endocrine, metabolic, reproductive, and cardiovascular systems. The recent epidemiologic literature shows some significant associations for PFHpA, for example, reductions in infant growth (Zhang et al., 2022b), cord blood leptin (Ding et al., 2023), cord blood gonadotropins (Nian et al., 2020), neonatal TSH (Guo et al., 2021), neurodevelopment scores in toddlers (Zhang et al., 2023), sperm concentration in young adulthood (Hærvig, K. K. et al., 2022), and adult serum bilirubin levels (Salihovic et al., 2018); increases in adult serum liver enzyme activities (Salihovic et al., 2018); sex-dependent decreases or increases in adiposity in children (Zhang et al., 2022a); and increases in the risks of developing chronic kidney disease (Xie et al., 2022), gestational diabetes (Kouiti et al., 2024), metabolic dysfunction-associated steatotic liver disease (Baumert et al., 2024), and autism spectrum disorder (Oh et al., 2022). The small number of epidemiology studies per outcome limits the ability to draw conclusions about the potential health hazards of PFHpA; however, the general findings identify potential areas of future research.

In summary, the liver was the primary target organ of PFHpA in rats and mice, and effects were also observed on the kidney, male reproductive endpoints, and on offspring development. Many human epidemiologic studies found associations between PFHpA exposure and potentially adverse effects on these and other systems. Alternative models suggest PFHpA may cause neurodevelopmental effects.

Selected Critical Effects and Approaches for TRV Derivation

The animal toxicity data are very limited for PFHpA, and the available studies report very different LOAELs. The lowest effect level is from the gestational exposure study in male mice (Zhou et al., 2023), which provides an oral LOAEL of 0.0015 mg/kg/day for effects on sperm parameters measured in the adult offspring (NOAEL not determined). The next lowest effect level is from the combined repeated dose oral toxicity study in mice with reproductive/developmental screening (Anonymous, 2017 cited in ECHA, 2020), which provides an oral LOAEL of 0.5 mg/kg/day for hepatocellular hypertrophy and necrosis observed in parental animals (NOAEL not determined). These two studies and the critical effects they identified are selected for derivation of candidate PODs and TRVs for screening-level risk assessment of PFHpA in this report (see Section 4.1.3).

Additionally, the POD (6.63 mg/kg/day) and composite uncertainty factor (50) recommended by UBA (2023) and the upper end of the RPF range (0.01–1) estimated by Bil et al. (2021) are both used to derive candidate TRVs for PFHpA in this report (see Section 4.1.3). For the RPF approach, the most recent agency TRV for PFOA (the EPA chronic RfD of 3×10^{-8} mg/kg/day; U.S. EPA, 2024b) was divided by the RPF estimated for PFHpA for hepatic effects (1) to derive a candidate TRV for PFHpA. Finally, because this chemical has limited toxicity data (i.e., no chronic data), a direct read-across approach was used as an alternative method to identify a TRV for PFHpA. Since different agencies recommended read across from either PFOA or PFOS for risk assessment of PFHpA, the TRV selected for read-across in this report is the EFSA TWI for the sum of PFOA, PFNA, PFHxS, and PFOS (4.4 ng/kg/week; EFSA, 2020), which was converted to a daily value (6×10^{-7} mg/kg/day) for read-across to PFHpA (see Section 4.1.3).

4.1.2.9. Perfluorooctanesulfonamide (PFOSA) (CASRN 754-91-6)

Previous Human Health Assessments

The only assessments identified for PFOSA used a read-across approach from PFOA or PFOS to estimate a safe exposure level for PFOSA (Swedish EPA, 2012; Danish EPA, 2015a; TCEQ, 2023).

The environmental protection agencies of Sweden and Denmark both used data for PFOS when deriving safe exposure levels for PFOSA (Swedish EPA, 2012; Danish EPA, 2015a). The Swedish assessment states, "Due to little toxicity data on PFOSA and the extensive metabolism to PFOS, data on PFOS will be used for the risk characterization" (Swedish EPA, 2012). The DNEL for hepatotoxicity for PFOSA was 162 ng/mL serum (based on an external dose NOAEL of 0.025 mg/kg/day for PFOS); the DNEL for PFOSA for reproductive toxicity was 196 ng/mL (Swedish EPA, 2012).

The Danish assessment derived tolerable daily intakes (TDIs) for PFOS and PFOA for the purposes of establishing limit concentrations in drinking water and other exposure media (Danish EPA, 2015a). The agency also considered exposure to PFOSA and states, "Sufficient data was not available for derivation of a specific TDI value for PFOSA. However, as the chemical structure of PFOSA is very comparable to PFOS (the amide derivate of PFOS) and as PFOSA is used as a precursor for PFOS formation it seems justifiable to apply the TDI for PFOS on PFOSA as well" (Danish EPA, 2015a). The TDI used for PFOSA was 3×10^{-5} mg/kg/day.

TCEQ (2023) used the chronic oral RfD they derived for PFOA (1.2×10^{-5} mg/kg/day) to estimate a safe exposure level for PFOSA on the basis that the two chemicals have similar acute oral lethal doses in rodents and their chemical structures both have an 8-carbon chain.

Hazard Identification

PFOSA is a precursor of PFOS in abiotic and biotic systems. The chemical structure of PFOSA is very similar to that of PFOS; both compounds have seven fully fluorinated carbons. The only difference between their structures is that PFOSA has a sulfonamide group attached to the terminal carbon whereas PFOS has a sulfonic acid group. PFOSA is metabolically transformed into PFOS and FOSA N-glucuronide in rats (Ross et al., 2012) and in vitro using human, rat, dog, and monkey liver microsomes (Xu et al., 2006). PFOSA has a long elimination half-life in rats (~2.5–5.9 days; Ross et al., 2012), but half-life data for PFOSA in humans is not available.

The only repeated dose study in mammals identified for PFOSA is a subchronic dietary study in rats that was primarily designed to collect toxicokinetic data. Ross et al. (2012) administered PFOSA to male rats via their diet for 77 days. The average daily intake of PFOSA over the course of the study was 83 ng/kg/day (0.000083 mg/kg/day), which was estimated based on food consumption (Ross et al., 2012). No mortality or overt signs of toxicity were observed, and there were no significant differences in growth rates or final body weights between the PFOSA-exposed and control animals (Ross et al., 2012). However, no other health endpoints were measured in this study, which makes it unusable for TRV derivation.

Other information on the toxic effects of PFOSA comes from alternative animal models, including several toxicity studies in zebrafish and in vitro assays investigating the toxic potency of PFOSA compared to other PFAS chemicals.

PFOSA was particularly bioactive in zebrafish studies, which reported that PFOSA caused adverse effects on zebrafish development, behavior, hepatic system, immune system, and cardiac morphology and function (Dasgupta et al., 2020; Britton et al., 2024; Truong et al., 2022; Xuan et al., 2024; Chen et al., 2024; Chen et al., 2022). Several zebrafish studies found that PFOSA was more potent than the other PFAS chemicals tested in the same systems. For example, PFOSA was the only PFAS chemical to alter both morphology and embryonic and larval behavior of zebrafish in a high-content screening study of 139 PFAS chemicals (Truong et al., 2022). Dasgupta et al. (2020) found that PFOSA was the most potent developmental toxicant of 38 PFAS chemicals tested, resulting in elevated mortality and abnormalities in zebrafish. Additionally, Xuan et al. (2024) found that PFOSA induced a greater hepatoxic response in zebrafish than PFOS, and Chen et al. (2024) found that PFOSA was more potent than PFOS in a bacterial challenge assay to test for immune effects in zebrafish. It is unknown whether these observations translate to a higher potency of PFOSA compared to PFOS in mammals, as experimental data are unavailable.

Some in vitro and ex vivo studies in mammalian cells also demonstrate a greater potency of PFOSA compared to more commonly tested PFAS chemicals including adverse effects

on neural cell differentiation (Slotkin et al., 2008) and inhibition of cytokine release from T-cells (Corsini et al., 2012). However, PFOSA was less potent than PFOS and PFOA in an in vitro thyroid hormone disruption assay (Behnisch et al., 2021) and it was inactive in a PPAR-α activation assay in human hepatocytes (Rosenmai et al., 2018).

Human epidemiologic studies have evaluated the possible associations between PFOSA exposure and many different health outcomes. Some significant associations were found for PFOSA, including increased risk of cardiovascular disease in NHANES participants (Huang et al., 2018), increased prevalence of lower respiratory tract infections in children (Impinen et al., 2018), decreased birth weight in boys (Robledo et al., 2015), increased impulsivity in children (Gump et al., 2011), and lower selective attention in children (Bach et al., 2022). Studies that investigated pregnancy outcomes did not find significant associations for PFOSA (Liu et al., 2024a), and results were mixed for studies that assessed fertility and fecundability (ATSDR, 2021). The small number of epidemiology studies per outcome limits the ability to draw conclusions about the potential health hazards of PFOSA; however, the general findings identify potential areas of future research.

In summary, the available toxicity data for PFOSA is inadequate for TRV derivation. Alternative models suggest it may be more toxic than other more commonly studied PFAS chemicals in those test systems, including for effects on development, neurodevelopment, and immune function, but it is unclear how that translates to human health impacts. Human epidemiologic studies have investigated several health outcomes for association with PFOSA and some studies found significant associations for PFOSA including neurodevelopmental outcomes.

Selected TRVs

The TRVs estimated by Danish EPA (2015a) (3×10^{-5} mg/kg/day) and TCEQ (2023) (1.2×10^{-5} mg/kg/day) are carried forward as candidate TRVs for PFOSA in this report (see Section 4.1.3). Additionally, the most recent EPA chronic RfD for PFOS (1×10^{-7} mg/kg/day; U.S. EPA, 2024a) was directly applied to PFOSA by read-across because PFOS is a metabolite of PFOSA (Ross et al., 2012).

4.1.3. TRV Derivation

We identified five chemicals that had official published agency TRVs: PFBA (EPA, 2022), PFHxA (EPA, 2023b), PFBS (EPA, 2021), DFE (EPA, 1994), and TFE (EPA, 1995). The RfDs and RfCs selected for these chemicals are shown in Table 11. For these chemicals, no further analysis was undertaken for TRV derivation as an authoritative source was identified.

Table 11. Selected Existing Agency Noncancer TRVs.

Chemical	Assessment Information	Critical Toxicity Endpoints	TRV Values
PFBA	2022 U.S. EPA chronic oral RfD	Hepatic and thyroid effects in rats (Butenhoff et al., 2012)	1×10^{-3} mg/ kg/day
PFHxA	2023 U.S. EPA chronic oral RfD	Decreased pup body weight in newborn rats (Loveless et al., 2009)	5×10^{-4} mg/kg/day
PFBS	2021 U.S. EPA chronic oral RfD	Decreased serum total T4 in newborn mice (Feng et al., 2017)	3×10^{-4} mg/kg/day
DFE	1994 U.S. EPA chronic inhalation RfC	No adverse effects observed (McAlack and Schneider, 1982)	40 mg/m^3
TFE	1995 U.S. EPA chronic inhalation RfC	Leydig cell hyperplasia for male rats (Collins et al., 1995)	80 mg/m^3

TRV = toxicity reference value; U.S. EPA = United States Environmental Protection Agency; RfD = reference dose; T4 = thyroxine; RfC = reference concentration.

For the remaining chemicals, 6:2 FTOH, 8:2 FTOH, PFHpA, and PFOSA, three sources of literature were identified to derive TRVs: (i) human health risk assessments literature, (ii) subchronic and developmental studies identified during the hazard identification phase, and (iii) read-across estimates of toxicity.

For each of the chemicals, we identified human health risk assessments associated with these chemicals (Table 12). Generally, agencies and authors took a variety of approaches to develop candidate TRVs, including alternative methods such as read-across. One common trend observed is that the majority of these assessments identify liver-related defects, such as hypertrophy, necrosis, and changes in liver weight, as the critical effects across chemicals. Interestingly, these assessments derived a wide range of values for each approach, spanning several orders of magnitude, which is likely related to differences in critical effect selection, study design, POD derivation methods, and the way uncertainty factors are applied.

To determine more standardized TRV values, we derived TRVs from the various subchronic and developmental studies identified during hazard identification (Table 13). From these assessments, two studies were not amenable to modeling, despite measuring suitable outcomes (Wang et al., 2019; Zhou et al., 2023), which was related to model failure as a consequence of dose spacing and experimental design.

Because of the data-poor nature of the chemicals, we also developed TRVs based on read-across extrapolations from chemicals similar to those of interest with readily available data and a TRV from an authoritative source. Results of the read-across extrapolations are found in Table 14. These data are generally lower in value than the TRVs derived from chemical-specific data but are more in line with values derived in agency

risk assessments that were also dependent on read-across approaches. Taken together, these findings suggest that read-across methods, particularly from the most toxic members of the class, PFOS and PFOA, result in more conservative risk values than those approaches dependent on chemical-specific data.

Table 12. Candidate TRVs Identified from Peer-Reviewed Assessments.

Assessment Name	Source Study	Study Design Chemical (Duration, Route of Exposure, Species)	Critical Effect	POD Method	POD Value (mg/kg/day)	Composite UF	TRV Value (mg/kg/day)
6:2 FTOH							
Bil et al. (2021)	Serex et al. (2014)	PFOA (90 day, oral, rats)	Absolute and relative liver weight	RPF with PFOA as anchor (50x less potent)	NA[a]	NA	2×10^{-6}
Rice et al. (2020)	Mukerji et al. (2015)	6:2 FTOH (one-generation reproduction, oral, mice)	Hepatocellular hypertrophy	NOAEL	1	300	3×10^{-3}
Cahuas et al. (2022); Danish EPA (2015b)	Serex et al. (2014)	6:2 FTOH (90 day, oral, rats)	Hematology and liver effects	NOAEL	5	1,000	5×10^{-3}
8:2 FTOH							
Bil et al. (2021)	Ladics et al. (2008)	8:2 FTOH (90 day, oral, rats)	Liver hypertrophy, absolute and relative liver weight	RPF with PFOA as anchor (25x less potent)	NA[b]	NA	8×10^{-7}
Himmelstein et al. (2012)	Ladics et al. (2008)	8:2 FTOH (90 day, oral, rats)	Liver necrosis	BMDL10 (HED)	1.04	2	5×10^{-1}
PFHpA							
Bil et al. (2021)	Multiple studies	PFOA, PFHxA (90 day, oral, rats)	PFOA, PFHxA (hepatotoxicity)	RPF with PFOA as anchor (100x less potent to 1x as potent)	NA[c]	NA	3×10^{-8}
TCEQ (2023)	Zeng et al. (2011)	PFOS (developmental, oral, rats)	PFOS (hippocampus synaptic structure)	RAX from PFOS (LOAEL)	0.6	26,300	2×10^{-5}
UBA (2023)	Anonymous (2017); ECHA (2020)	PFHpA (90 day, oral mice)	Liver necrosis in P_0 males	BMDL5	6.63	50	1×10^{-1}

Assessment Name	Source Study	Study Design Chemical (Duration, Route of Exposure, Species)	Critical Effect	POD Method	POD Value (mg/kg/day)	Composite UF	TRV Value (mg/kg/day)
PFOSA							
TCEQ (2023)	PFOA (Macon et al., 2011)	PFOA (developmental, oral, mice)	PFOA (mammary gland development)	RAX from PFOA (LOAEL)	0.3	24,300	1×10^{-5}
Danish EPA (2015a)	PFOS (Thomford et al., 2002)	PFOS (2 yr, oral, rats)	PFOS (liver histopathology)	RAX from PFOS (BMDL10)	0.033	1,230	3×10^{-5}

POD = point of departure; UF = uncertainty factor; TRV = toxicity reference value; PFOA = perfluorooctanoic acid; RPF = relative potency factor; NA = not applicable; NOAEL = no-observed-adverse-effect level; BMDL10 = lower confidence interval of the benchmark dose for a 10% effective level; HED = human equivalent dose; RAX = read-across; LOAEL = lowest-observed-adverse-effect level; BMDL5 = lower confidence interval of the benchmark dose for a 5% effective level.

[a]For this chemical, RPF analysis was conducted on the TRV not the POD. Thus, the most recent TRV derived for PFOA (3×10^{-8} mg/kg/day) in the U.S. EPA 2024 Assessment was used to calculate the proposed 6:2 FTOH TRV value by dividing the PFOA TRV by the RPF (0.02) for this chemical.

[b]For this chemical, RPF analysis was conducted on the TRV not the POD. Thus, the most recent TRV derived for PFOA (3×10^{-8} mg/kg/day) in the U.S. EPA 2024 Assessment was used to calculate the proposed 8:2 FTOH TRV value by dividing the PFOA TRV by the RPF (0.04) for this chemical.

[c]For this chemical, RPF analysis was conducted on the TRV not the POD. Thus, the most recent TRV derived for PFOA (3×10^{-8} mg/kg/day) in the U.S. EPA 2024 Assessment was used to calculate the proposed PFHpA TRV value by dividing the PFOA TRV by the RPF (1–0.01) for this chemical.

Table 13. Candidate TRVs Developed from Critical Effects.

Toxicity Study	Study Design - Duration, Route of Exposure, Species (Exposure Paradigm)	Critical Effects Identified	POD Method	POD Value (mg/kg/day)	Composite UF	TRV Value (mg/kg/day)
6:2 FTOH						
Mukerji et al. (2015)	One-generation reproductive, oral, mice (107–109 days males, 70 days premating–LD 21 females)	Male hepatocellular hypertrophy	NOAEL	1	300 (UFH = 10, UFA = 10, UFS = 3)	3×10^{-3}
		Female hepatocellular hypertrophy	BMDL10	1.001	300 (UFH = 10, UFA = 10, UFS = 3)	3×10^{-3}
Xia et al. (2023)	Developmental, oral, mice (GD 12.5–21.5)	Reproductive effects in male offspring[a]	LOAEL	5	1,000 (UFH = 10, UFA = 10, UFL = 10)	5×10^{-3}
Xia et al. (2024)	Developmental, oral, mice (GD 8.5–delivery)	Anxiety-like behavior and impairment in learning memory in offspring	LOAEL	5	1,000 (UFH = 10, UFA = 10, UFL = 10)	5×10^{-3}
8:2 FTOH						
Ladics et al. (2008)	90 day, oral, rat	Male thyroid gland colloid alteration (no high dose)	BMDL10	0.101	300 (UFH = 10, UFA = 10, UFS = 3)	3×10^{-4}
		Male liver focal necrosis	BMDL10	1.636	300 (UFH = 10, UFA = 10, UFS = 3)	5×10^{-3}
		Female kidney nephropathy	BMDL10	3.7188	300 (UFH = 10, UFA = 10, UFS = 3)	1×10^{-2}
		Male absolute liver weight	BMDL10	9.81	300 (UFH = 10, UFA = 10, UFS = 3)	3×10^{-2}

Toxicity Study	Study Design – Duration, Route of Exposure, Species (Exposure Paradigm)	Critical Effects Identified	POD Method	POD Value (mg/kg/day)	Composite UF	TRV Value (mg/kg/day)
PFHpA						
Anonymous (2017) reported in ECHA (2020)	Combined 90 day with reproduction/developmental screening, oral, mice (109–113 days males, 90 days premating–LD 20 females)	Liver necrosis in P_0 males	BMDL10	8.48	300 (UFH = 10, UFA = 10, UFS = 3)	3×10^{-2}
		Hepatocellular hypertrophy in P_0 and F_1 males and females	LOAEL	0.5	3,000 (UFH = 10, UFA = 10, UFS = 3, UFL = 10)	2×10^{-4}
Zhou et al. (2023)	Developmental, oral, mice (GD 1–16)	Reproductive effects in male offspring[b]	LOAEL	0.0015	1,000 (UFH = 10, UFA = 10, UFL = 10)	2×10^{-6}

POD = point of departure; UF = uncertainty factor; TRV = toxicity reference value; LD = lactation day; NOAEL = no-observed-adverse-effect level; UFH = uncertainty factor to account for intraspecies differences; UFA = uncertainty factor to account for interspecies differences; UFS = uncertainty factor to account for extrapolation from subchronic to chronic duration; BMDL10 = lower confidence interval of the benchmark dose for a 10% effective level; GD = gestation day; LOAEL = lowest-observed-adverse-effect level; UFL = uncertainty factor to account for the use of a LOAEL instead of a NOAEL or benchmark dose lower confidence limit.

[a]Delayed preputial separation, reduced anogenital distance, reduced epididymal sperm count and sperm viability, increased rate of sperm abnormality.

[b]Sperm count, sperm concentration, total cell count, sperm progressive cells' head area.

Table 14. Read-Across TRVs Based on Hazard Identification.

Target Chemical	Source Chemical	Assessment Name	Study Details with Critical Effects	TRV Value (mg/kg/day)
6:2 FTOH	PFHxA	U.S. EPA (2023b) RfD	Derived from Loveless et al., 2009; decreased pup body weight in newborn rats	5×10^{-4}
8:2 FTOH	PFOA	U.S. EPA (2024b) RfD	Derived from multiple studies; decreased serum anti-tetanus and anti-diphtheria antibody concentration in children, decreased birth weight in infants, increased serum total cholesterol in adults	3×10^{-8}
PFHpA	Composite of PFOA, PFNA, PFHxS, and PFOS	EFSA (2020) TWI[a]	Derived from Abraham et al., 2020; decreased diphtheria antibody response after vaccination	6×10^{-7}
PFOSA	PFOS	U.S. EPA (2024a) RfD	Derived from multiple studies; decreased birth weight in infants, increased serum total cholesterol in adults	1×10^{-7}

TRV = toxicity reference value; U.S. EPA = United States Environmental Protection Agency; RfD = reference dose; PFOA = perfluorooctanoic acid; PFNA = perfluorononanoic acid; PFHxS = perfluorohexanesulfonic acid; PFOS = perfluorooctane sulfonic acid; EFSA = European Food Safety Authority; TWI = tolerable weekly intake.
[a]The TWI derived by EFSA (4.4 ng/kg/week) was converted to a daily intake in mg/kg/day for read-across to PFHpA.

4.1.4. TRV Selection

To perform traditional risk assessment, a single TRV is identified from the candidate TRVs for each chemical. However, building on work performed under a previous call order under this contract (Call Order No. 61320623F2030), we utilized a probabilistic approach for this screening-level risk assessment that does not depend on a single value. Instead, a distribution of values can be used to bound the potential occurrence of hazard, given the uncertainty in the estimate. The bounds and central tendency for these distributions can be found in Table 15. Considering the available data for each chemical, the following approaches were undertaken:

- Authoritative Source: For official agency assessments conducted by the EPA, the central estimate was assumed to be the value reported by the EPA. To determine the bounds of the range we multiplied the TRV by 3 for the 5th percentile and divided by 3 for the 95th percentile, as the official definition of the TRV is that it is a value centered in a distribution that spans 1 order of magnitude (Krithikadatta, 2014; U.S. EPA, 2002). As the distribution is assumed to span an order of magnitude equally on either side, a normal distribution shape is assumed.
- Single TRV Selected: If candidate TRVs were developed based on chemical-specific data and at least two independent chemical-specific studies showed agreement in the derived value, the best estimate value based on professional judgment was selected as the central tendency value for the TRV. The 5th percentile was defined by the lowest candidate TRV value and the 95th percentile

was defined by the highest candidate TRV value. A log normal shape was chosen to provide a right-skew to center the distribution values at the lower end of values, rather than at the higher end of values, to be more health protective.

- No TRV Selected: If no chemical-specific data existed (PFOSA) or chemical-specific data were limited to a few studies (PFHpA), no central tendency was chosen. The highest and lowest candidate values were used to define the bounds of the distribution. A log normal shape was chosen to provide a right-skew to center the distribution values at the lower end of values, rather than at the higher end of values, to be more health protective.

Table 15. Final TRVs Selected and Parameterization of the Bounds of the Distribution.

Chemical (units)	TRV Central Tendency	TRV P5	TRV P95	Distribution Shape
Official Agency Assessment TRVs				
PFBA (mg/kg/day)	1×10^{-3}	3×10^{-4}	3×10^{-3}	Normal
PFHxA (mg/kg/day)	5×10^{-4}	2×10^{-4}	2×10^{-3}	Normal
PFBS (mg/kg/day)	3×10^{-4}	1×10^{-4}	9×10^{-4}	Normal
DFE (mg/m^3)	40	13	120	Normal
TFE (mg/m^3)	80	27	240	Normal
Single TRV Selected				
6:2 FTOH (mg/kg/day)	3×10^{-3}	2×10^{-6}	5×10^{-3}	Log normal
8:2 FTOH (mg/kg/day)	3×10^{-4}	3×10^{-8}	5×10^{-1}	Log normal
No TRV Selected				
PFHpA (mg/kg/day)	NA	3×10^{-8}	1×10^{-1}	Log normal
PFOSA (mg/kg/day)	NA	1×10^{-7}	3×10^{-5}	Log normal

TRV = toxicity reference value; P5 = 5th percentile; P95 = 95th percentile; NA = not applicable.

4.1.5. Uncertainties and Limitations

The main limitation of this hazard assessment is that only noncancer outcomes were evaluated because the data available to assess the cancer hazards of these chemicals in animals and humans were inadequate. This limitation is significant given that IARC has concluded PFOA is carcinogenic to humans and PFOS is possibly carcinogenic to humans (IARC, 2025) and several of the targeted PFAS chemicals are similar in chemical structure and toxicological profile to those chemicals.

The other major limitation is the limited chemical-specific data. Two of the chemicals, PFOSA and PFHpA, have only one or a few chemical-specific toxicity studies, respectively. As such, no single TRV could be selected and the bounding of the TRV distribution is reliant on the nonchemical-specific information derived from the read-

across assessment. For 6:2 FTOH and 8:2 FTOH, there is sufficient information on subchronic and developmental toxicity by the oral route of exposure, but there is a lack of animal studies by other routes of exposure and studies evaluating chronic toxicity, multigenerational reproductive toxicity, and sensitive endpoints of concern for PFAS chemicals, such as immunotoxicity and mammary gland development. The FTOHs also lack studies evaluating subchronic or chronic inhalation exposure even though this is an important route of exposure in humans.

4.2. Exposure

4.2.1. Background Exposures

4.2.1.1. Pooled Background Concentrations and Doses

Relevant pathways for background exposure include drinking water ingestion, soil ingestion, dietary ingestion, and inhalation of outdoor air. Fifty studies were identified with concentration data for at least one targeted PFAS chemical in drinking water, soil, or outdoor air. Data sets that reported (i) only chemical loadings (and not concentrations), (ii) ranges or inequalities (such as mean <5 ng/m^3), or (iii) inconsistent concentration data (e.g., the reported minimum was higher than the median) were excluded. Each data set was assumed to have a log normal distribution and therefore a normal distribution was fitted in log space. The fit was transformed back to regular space to obtain the GM, geometric standard deviation (GSD), 5th percentile (P5), and P95. To obtain pooled statistics, data sets were first categorized into bins based on source type (i.e., general population or highly exposed). A pooled GM (or other statistic) was then calculated as a weighted mean of the individual GMs using the number of samples as the weighting factor, for each chemical-bin combination. For this report, only general population results are discussed because highly exposed data sets were not available for all chemical-media combinations.

Table 16 presents the pooled GM and P95 concentrations for each of the targeted PFAS chemicals in outdoor air, drinking water, and soil. For the two FTOHs, no studies were identified that reported drinking water concentrations, likely due to their transformation from FTOHs to PFCAs. Instead, the method detection limit of 2.16 and 10.8 ng/L in tap water for 6:2 FTOH and 8:2 FTOH, respectively, from Habib et al. (2023) was used as a surrogate for both the GM and P95. For DFE and TFE, no data sets were identified that reported concentrations for any of the three media.

Table 16. Pooled Geometric Mean and 95th Percentile Concentration of Targeted PFAS Chemicals in Outdoor Air, Drinking Water, and Soil.

	Outdoor Air (ng/m^3)			Drinking Water (ng/L)			Soil (ng/g)		
Chemical	n	Pooled GM	Pooled P95	n	Pooled GM	Pooled P95	n	Pooled GM	Pooled P95
6:2 FTOH	40	0.021	0.069	1	2.16[a]	2.16[a]	3	0.62	2.89
8:2 FTOH	46	0.042	0.13	1	10.8[a]	10.8[a]	3	0.23	1.23
PFOSA	6	0.0044	0.020	2	0.021	0.19	1	0.013	0.11
PFBA	3	0.0013	0.0098	29	3.33	31.3	2	1.08	2.06
PFHpA	19	1.08	3.39	30	4.40	13.8	12	0.56	1.75
PFHxA	14	29.0	90.7	42	3.10	8.58	15	0.48	2.84
PFBS	9	1.42	4.43	49	2.73	12.2	10	5.85	18.4
DFE	–[a]	–	–	–	–	–	–	–	–
TFE	–	–	–	–	–	–	–	–	–

n = number of data sets; GM = geometric mean; P95 = 95th percentile.
[a]No data sets were identified in the SEMs, existing assessments, peer-reviewed literature search, or targeted search.

The average daily dose derived from the pooled GM concentrations are presented in Table 17 and Figure 2 for infants (<1 year) and adults for outdoor air inhalation, drinking water ingestion, and soil ingestion. For simplicity, we assumed that the outdoor air concentrations were completely absorbed if inhaled, whether the chemical is in gas or particulate phase. Doses for the fourth relevant pathway, dietary ingestion, were extracted from an existing assessment. EFSA (2020) estimated chronic dietary exposure to several PFAS chemicals, including PFOSA, PFBA, PFHpA, PFHxA, and PFBS, for which the mean and 95th percentile exposures were calculated per dietary survey and age group using a lower bound and upper bound approach. In the lower bound approach, a value of zero is assigned to samples reported as lower than the limit of detection (LOD) or limit of quantification (LOQ), while in the upper bound approach, the LOD value is assigned to samples reported as <LOD or <LOQ. For this report, we used EFSA's upper bound median value across surveys as our dietary dose, which provides a more conservative estimate than the lower bound approach. The doses used are presented in Table 17 and Figure 2 for infants and adults. Doses for all other age groups will generally fall between these two values.

For 6:2 and 8:2 FTOH, no data sets were identified that reported their concentrations in food. EFSA (2020) did identify occurrence data for 8:2 FTOH in food but dietary exposure was not assessed because the data did not meet their evaluation and validation criteria. Specifically, the European Commission Recommendation 2010/161/EC recommends an LOQ of 1 μg/kg for monitoring PFAS chemicals in food and for 8:2 FTOH, all results were obtained using a method with an LOQ >1 μg/kg. Additionally, all results were below the

LOQ or LOD and thus the occurrence data were not used. While EFSA (2020) did not evaluate 6:2 FTOH, it is likely that the results would be similar. As such, we assumed that the two FTOHs were not likely in food and set the dietary dose to zero. This assumption does not include PFAS migration from food contact materials into food.

For both infants and adults, central tendency aggregate background exposure ranged from approximately 3×10^{-6} to 3×10^{-5} mg/kg/day for PFOSA, PFBA, PFHpA, PFHxA, and PFBS. The dominant pathway was dietary ingestion, which contributed >95% of the total background for PFOSA, PFBA, PFHpA, and PFBS. Dietary ingestion was also a primary contributor for PFHxA (87% and 70% for infants and adults, respectively) with inhalation of outdoor air accounting for almost the remainder. For 6:2 FTOH and 8:2 FTOH for which the dietary dose was zero, the aggregate background exposure was lower, ranging from approximately 4×10^{-8} to 9×10^{-7} mg/kg/day and was primarily (>97%) due to drinking water ingestion. However, the drinking water doses were based on LOD values and therefore actual doses are likely to be lower. Background exposures by pathway are available for additional age groups in Supplemental File F and show similar trends.

Table 17. Central Tendency[a] Background Exposures for Individual and Combined Pathways (mg/kg/day) for Infants (<1 Year) and Adults.

Chemical	Age Group	Outdoor Air	Drinking Water	Soil	Diet	Aggregate Background
6:2 FTOH	Infant	1.63×10^{-9}	1.86×10^{-7}	1.99×10^{-9}	0	1.90×10^{-7}
	Adult	1.11×10^{-9}	3.70×10^{-8}	7.76×10^{-11}	0	3.82×10^{-8}
8:2 FTOH	Infant	3.20×10^{-9}	9.31×10^{-7}	7.31×10^{-10}	0	9.35×10^{-7}
	Adult	2.18×10^{-9}	1.85×10^{-7}	2.85×10^{-11}	0	1.87×10^{-7}
PFOSA	Infant	3.32×10^{-10}	1.81×10^{-9}	4.31×10^{-11}	2.90×10^{-5}	2.90×10^{-5}
	Adult	2.27×10^{-10}	3.59×10^{-10}	1.68×10^{-12}	8.63×10^{-6}	8.63×10^{-6}
PFBA	Infant	9.84×10^{-11}	2.87×10^{-7}	3.47×10^{-9}	7.28×10^{-6}	7.57×10^{-6}
	Adult	6.71×10^{-11}	5.70×10^{-8}	1.35×10^{-10}	2.52×10^{-6}	2.58×10^{-6}
PFHpA	Infant	8.27×10^{-8}	3.80×10^{-7}	1.81×10^{-9}	1.47×10^{-5}	1.52×10^{-5}
	Adult	5.65×10^{-8}	7.54×10^{-8}	7.06×10^{-11}	2.42×10^{-6}	2.56×10^{-6}
PFHxA	Infant	2.21×10^{-6}	2.67×10^{-7}	1.56×10^{-9}	1.67×10^{-5}	1.92×10^{-5}
	Adult	1.51×10^{-6}	5.31×10^{-8}	6.06×10^{-11}	3.60×10^{-6}	5.16×10^{-6}
PFBS	Infant	1.08×10^{-7}	2.35×10^{-7}	1.88×10^{-8}	1.75×10^{-5}	1.78×10^{-5}
	Adult	7.38×10^{-8}	4.67×10^{-8}	7.31×10^{-10}	3.57×10^{-6}	3.69×10^{-6}
DFE	Infant	–[b]	–	–	–	–
	Adult	–	–	–	–	–
TFE	Infant	–	–	–	–	–
	Adult	–	–	–	–	–

[a]Central tendency exposures calculated from pooled geometric mean concentrations.
[b]Doses were not calculated because concentration data were not available.

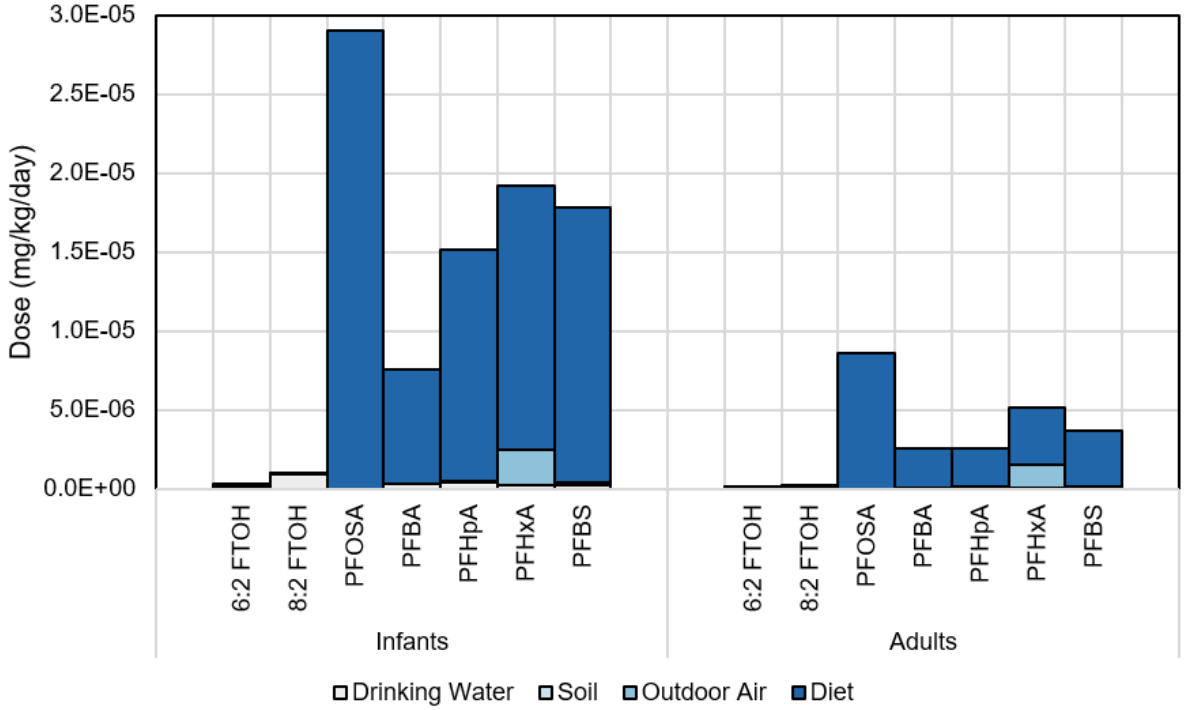

Figure 2. Estimated Central Tendency Background Exposure for Residential General Population Infants and Adults by Chemical and Pathway.

4.2.1.2. Uncertainties and Limitations

In general, uncertainties in the estimated background exposures were due to data availability with fewer than five data sets available for several chemical-media combinations. For 6:2 and 8:2 FTOH, LODs were used as surrogate concentrations for drinking water, leading to a likely overestimate of exposure due to drinking water ingestion. On the other hand, in the absence of concentration data in food for 6:2 and 8:2 FTOH, we assumed a dietary dose of zero; however, there may be potential exposure due to migration from food packaging into food.

For all data, (pooled) central tendency values were calculated by fitting the data in log space and using the fitted median for our dose estimates. At times, this approach resulted in differences between the study-reported and fitted medians for chemical-media combinations with only one data set. Different choices are available for calculating a central tendency value (e.g., study-reported medians can be averaged to obtain a pooled value) and selecting a central tendency value (e.g., arithmetic mean versus geometric mean), which can result in different doses calculated.

To calculate dose, we applied inhalation and ingestion absorption fractions of 1 for all chemicals, similar to DeLuca et al. (2022), which provides a conservative estimate of exposure. For our dose calculations, we assumed that all outdoor air concentrations were in gas phase. However, gas and particulate phase concentrations can be separated, with

separate absorption fractions applied, wherein the latter is chemical dependent (i.e., if the chemical is particle bound). Exposure factors such as body weight and inhalation rate were set to single values for each age group but could be varied in future analyses.

4.2.2. Consumer Exposures Estimated from Mechanistic Models

4.2.2.1. Product Use Categories

Twenty-seven PUCs with weight fraction data for at least one targeted PFAS chemical were identified from the Holder et al. (2023) and Dewapriya et al. (2023) review articles and the default SHEDS-HT input files. Table 18 shows the chemical-PUC combinations that were modeled. In general, more than 10 PUCs were modeled for each PFAS chemical, with the exception of PFOSA, DFE, and TFE, for which only 3, 5, and 1 PUC were modeled, respectively.

Table 18. Combinations of Chemical-Product Use Categories Modeled (x = present | - = absent) .

PUC	Description	6:2 FTOH	8:2 FTOH	PFBA	PFHxA	PFHpA	PFBS	PFOSA	DFE	TFE
A.BM.CTG	Coatings	x	x	x	x	x	x	–[a]	–	–
A.ET.LET	Large electronics	–	–	–	x	–	x	–	–	–
A.ET.SET	Small electronics	–	–	–	x	x	x	–	–	–
A.TX.BDD	Bedding	–	–	x	x	x	x	–	–	–
A.TX.CAR	Car textiles	–	x	–	x	x	x	–	–	–
A.TX.CPT	Carpet	x	x	x	x	x	x	x	–	–
A.TX.CRT	Curtains	–	–	–	–	–	x	–	–	–
A.TX.FRN	Furniture	x	x	x	x	x	x	x	–	–
A.TX.INC	Inner clothing	x	x	x	x	x	x	–	–	–
A.TX.ODC	Outdoor clothing	x	x	x	x	x	x	x	–	–
A.TX.TXT	Textile toy	–	–	–	–	–	x	–	–	–
A.TX.VYF	Vinyl flooring	–	–	x	x	x	–	–	–	–
P.AC.010.999	Arts and crafts adhesive	–	–	–	–	–	–	–	x	–
P.AP.110.999	Body wax (car)	x	x	x	x	x	–	–	–	–
P.AP.140.000	Motor oil	–	–	x	x	x	x	–	–	–
P.HM.020.000	Caulk or sealant	–	x	–	–	–	–	–	–	–
P.HM.090.999	Lubricant	x	x	x	x	x	x	–	–	–
P.HM.110.999	Multipurpose adhesive	x	x	x	x	x	–	–	x	–
P.HM.120.009	Paint (interior)	x	x	x	x	x	x	–	–	–
P.IH.010.999	Air freshener	–	–	–	–	–	–	–	x	–

PUC	Description	6:2 FTOH	8:2 FTOH	PFBA	PFHxA	PFHpA	PFBS	PFOSA	DFE	TFE
P.IH.030.999	Automatic dishwashing detergent	x	x	x	–	–	–	–	–	–
P.IH.070.999	Carpet cleaner	x	x	x	x	x	x	–	x	–
P.IH.140.999	Electronics cleaner	–	–	–	–	–	–	–	x	x
P.IH.200.000	Floor polish	x	x	x	x	x	x	–	–	–
P.IH.330.000	Shoe polish or protectant	–	–	–	x	–	–	–	–	–
P.IH.SKI	Ski polish	x	x	x	x	x	x	–	–	–
P.LY.010.005	Cleaner (exterior)	–	–	–	–	x	–	–	–	–
	Total PUCs	13	15	16	19	18	17	3	5	1

PUC = product use category.
[a]No product uses were identified and/or no weight fraction data were available.

4.2.2.2. Aggregate Consumer Exposures

As previously described in Section 3.3.2.1, the population mean and standard deviation of the product users from the SHEDS-HT runs, which models 1 day of exposure, can be used as a surrogate for chronic exposure of users. The chronic average daily dose (CADD) for all chemicals is presented in Supplemental File E. All model runs were conducted for 100,000 simulated persons and the chemical prevalence (probability the product/article has the chemical) was set to 1. Postprocessing was then conducted on the SHEDS-HT outputs using the "all individuals" file to calculate population statistics for the subpopulation of simulated individuals with non-zero product exposures, specifically for individuals that use at least one product (i.e., users of at least one article but no products were not included). Focusing only on product users and setting the chemical prevalence to 1 results in an overestimation of CADD; however, we purposefully chose this overestimation because for estimating risk, the TRVs used are derived based on animal toxicity studies during which the animal is exposed to the chemical and therefore the exposure estimates should also correspond to an exposed population. Exposure from articles was generally lower than from products and therefore we focused on product users. In some instances, if no products were used, then the doses from articles only were used.

Final CADD values represent the aggregate consumer exposure (i.e., across all PUCs) and were reported for the three age groups: 0–5 years, 6–11 years, and 12–99 years – defined in the default input files. Figure 3 presents the estimated doses by age group. Within a chemical, doses were generally within one order of magnitude across the three age groups. Central tendency doses were highest in the youngest age group and lowest in the oldest age group for all chemicals. Doses for the 0–5 years group ranged from 3.1×10^{-5} to 6.4×10^{-4} mg/kg/day for the two FTOHs (6:2 and 8:2) and the three acids (PFBA, PFHpA, and PFHxA) and were in the 10^{-7} mg/kg/day range for PFBS and PFOSA. The lower doses for PFBS and PFOSA were because children 0–5 years old did not use any of the products that contained these chemicals (PFBS) or there were only articles (no products) reported with the chemical (PFOSA) and therefore the dose for this group was due only to exposure to articles. Children 0–5 years old also did not use any products containing DFE or TFE. For the 12–99 years group, doses ranged from 2.8×10^{-6} to 2.2×10^{-4} mg/kg/day for all chemicals except PFOSA. The estimated dose of 4.3×10^{-8} mg/kg/day for PFOSA was relatively low because it was present in only three article PUCs and no product PUCs.

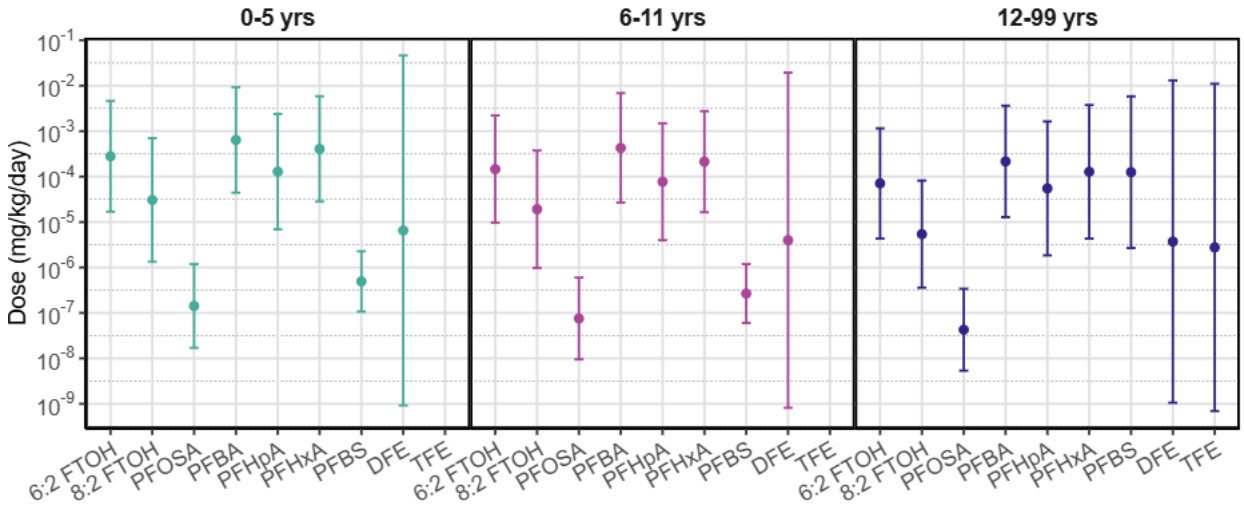

Figure 3. SHEDS-HT Estimated Central Tendency and Upper and Lower Values for Aggregate Consumer Exposure by Age Group and Chemical.

Geometric mean estimates; lower and upper whiskers represent the 5th and 95th percentiles, respectively.

The % contribution of each PUC to total exposure was estimated using the SHEDS-HT "source means" output file, which provides a breakdown of chemical exposure by PUC across all simulated individuals (for all ages). In general, for all chemicals except 8:2 FTOH, one PUC accounted for >50% of total exposure with other PUCs ranging from negligible to minor contributions. For example, Figure 4a, for PFHpA, shows that interior paint contributed to 62% of the total exposure, with carpet, coatings, and vinyl flooring contributing 5% to 11% each. The remaining 14 PUCs accounted for 15% of total exposure with each individual PUC contributing <5%. For 8:2 FTOH, there was no single PUC that accounted for >50% of total exposure. Instead, four PUCs had contributions that ranged from 14% to 29%, which when summed together accounted for 81% of total exposure. The remaining 11 PUCs had individual contributions <5% (see Figure 4b). For PFOSA, data were available for only three PUCs, with all three having >10% contributions (see Figure 4c).

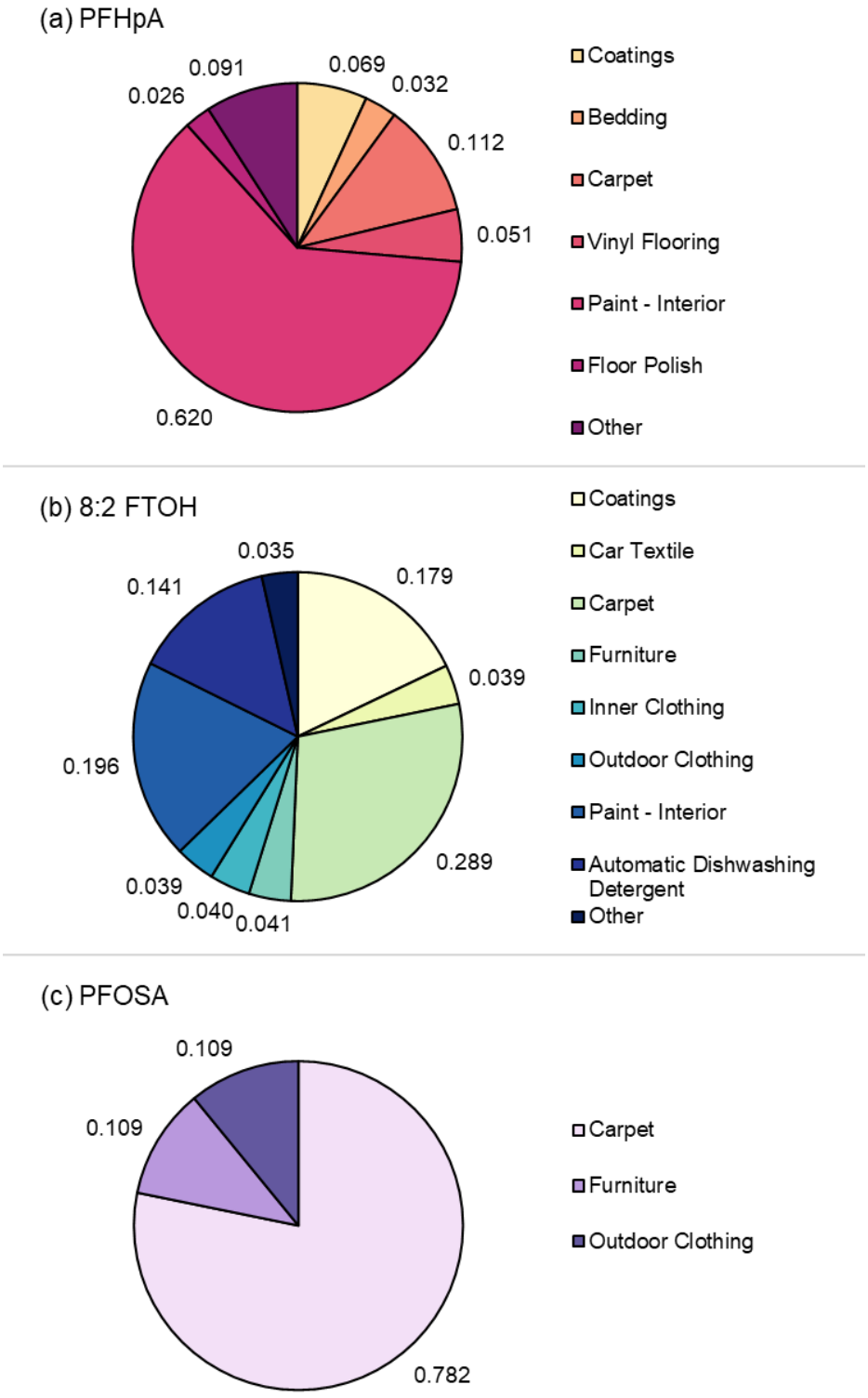

Figure 4. Contribution by PUC to Aggregate Consumer Exposure Estimated by SHEDS-HT for (a) PFHpA, (b) 8:2 FTOH, and (c) PFOSA.

PUCs with <2% contribution to total exposure were grouped together under "Other."

4.2.2.3. Aggregate Total Exposures

Aggregate total exposures can be estimated by combining the aggregate consumer exposures from SHEDS-HT with background exposures (dietary ingestion, drinking water ingestion, soil ingestion, and inhalation of outdoor air) calculated in Section 4.2.1.1. Background exposures for infant (<1 year), child (6–10 years), and adult (21–78 years) were combined with the SHEDS-HT age groups of 0–5, 6–11, and 12–99 years, respectively. For central tendency values, Figure 5 shows that with the exception of PFOSA (for all age groups) and PFBS (for infants and children), total exposure was predominantly the result of consumer exposure rather than background exposure. For the exceptions mentioned above, background exposure was higher because infants and children did not use any of the products that contained these chemicals (PFBS) or there were only articles (no products) reported with the chemical (PFOSA).

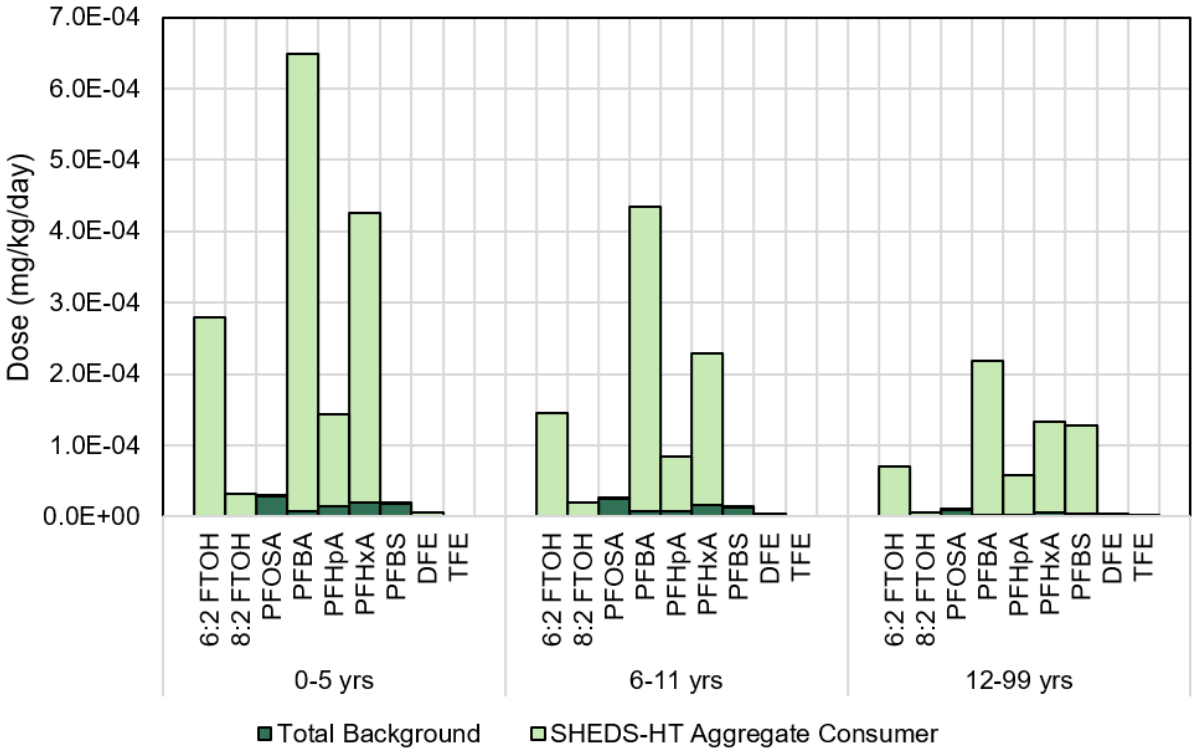

Figure 5. Estimated Central Tendency Background + Consumer Exposure by Age Group and Chemical.

4.2.2.4. Uncertainties and Limitations

The PUCs modeled for each chemical were identified using three data sources: Holder et al. (2023), Dewapriya et al. (2023), and the SHEDS-HT default input files, with the requirement that product concentration data (i.e., weight fractions) must be available in order to model the PUC (i.e., we did not assume or estimate concentrations). As a result, the number of PUCs modeled was limited by data availability (e.g., PFOSA only had data

for three articles) and there is uncertainty about whether all products with the targeted PFAS chemicals were captured. In addition, consumer product data published after April 2023 were not captured. Holder et al. (2023) downloaded search results directly from the EPA's Health and Environmental Research Online database and filtered the studies to ones that were published between 2003 and 2020 (or 2021, depending on the chemical), whereas the Dewapriya et al. (2023) review article conducted searches between August 2022 and April 2023 and refined the search results to within the last 10 years of their search.

For PUCs with weight fraction data, the number of data sets for each PUC varied, with some chemical-PUC combinations having only one data set while others had a large number of data sets (e.g., for 8:2 FTOH, there was one data set for car textiles versus 45 data sets for carpets). In the case of chemical-PUC combinations with only one or two data sets, the weight fractions used in our modeling runs may not represent the full range of actual values found in products. Other than weight fractions and chemical prevalence (discussed in the next paragraph), the model inputs were taken from the default input files or revised based on professional judgment. However, additional adjustments could be made. For example, interior paint had the highest contribution to total consumer exposure for several chemicals. We modeled interior paint assuming that 43% of homes are painted each year, typically using 1,300 g of paint with a painting duration of 2 hours and a room volume of 24 m^3. The house prevalence of 43% (taken from the default input file) and the use frequency of 1/year (lowered from the default input file) are likely overestimates and could be further adjusted if needed. Updated consumer surveys on interior house paint (or other PUC) variables would be useful in verifying or adjusting these model inputs, but a larger effect likely comes from the assumptions about chemical prevalence discussed in the next paragraph.

Finally, the modeled doses likely somewhat overestimate exposure for the entire population because (i) we set the chemical prevalence to 1, meaning that all products/articles modeled contained all targeted PFAS chemicals and (ii) we report doses for only the subpopulation of simulated individuals with non-zero product exposures. In reality, not all products will contain the targeted chemicals, as seen from the Holder et al. (2023) database in which, for example, PFBA and PFHxA were reported as not detected in some carpet samples and detected in others. However, these higher exposures are more representative for a smaller population group of people who are users of these products containing these chemical substances. This reference group is useful and of special interest to CPSC staff for comparison with other population groups.

To determine the weight fractions to use for our model runs, we included only data sets with detectable concentrations of our targeted PFAS chemicals. The inclusion of non-detects would lower the average chemical weight fractions. Similarly, we purposefully focused only on product users even though our SHEDS-HT model outputs show simulated individuals that do not use any of the products that contain our targeted PFAS chemicals (although they may use articles containing them). If all simulated individuals were included (i.e., individuals that use at least one product, individuals that use at least one article or product, and individuals that do not use any product or article that contain the targeted PFAS chemicals), the estimated doses would be at least an order of magnitude lower (see Supplemental File E for full SHEDS-HT results). The choice to focus on product users and set the chemical prevalence to 1 was previously discussed in Section 4.2.2.2.

4.2.3. Exposures Estimated from Monitoring Data/Empirical Measurements

Thirty-seven studies were identified with concentration data for at least one targeted PFAS chemical in indoor air and indoor dust. One study was identified with skin wipe data and two studies were identified with migration data into saliva. In the sections below, the contribution of each pathway to total exposure is discussed, for which total exposure is the sum of all indoor air and dust-related pathways, direct dermal contact, mouthing, and all background pathways.

4.2.3.1. Indoor Air and Dust-Related Pathways

For indoor air and indoor dust, data sets were first categorized into bins based on source type (i.e., general population or highly exposed) and indoor environment (i.e., residential, commercial, school, vehicle, mixed use) before pooled statistics were calculated. For this report, only general population residential results are discussed, due to the limited number of data sets available for the other categories. Data processing followed the approach outlined for background monitoring data (see Section 4.2.1.1). Table 19 presents the pooled GM and P95 concentrations for each of the targeted PFAS chemicals in indoor air and indoor dust.

Table 19. Pooled Geometric Mean and 95th Percentile Concentration of Targeted PFAS Chemicals in Indoor Air and Indoor Dust.

	Indoor Air (ng/m^3)			Indoor Dust (ng/g)		
Chemical	n	Pooled GM	Pooled P95	n	Pooled GM	Pooled P95
6:2 FTOH	14	1.37	5.23	18	24.7	484.7
8:2 FTOH	22	4.07	24.5	22	71.8	486.5
PFOSA	3	0.016	0.20	18	15.7	393.9

Chemical	Indoor Air (ng/m³)			Indoor Dust (ng/g)		
	n	Pooled GM	Pooled P95	n	Pooled GM	Pooled P95
PFBA	1	0.0036	0.047	17	4.75	104.5
PFHpA	5	0.0048	0.021	19	32.2	213.3
PFHxA	6	0.0088	0.047	30	15.0	215.6
PFBS	3	0.00086	0.063	24	3.82	23.2
DFE	–[a]	–	–	–	–	–
TFE	–	–	–	–	–	–

n = number of data sets; GM = geometric mean; P95 = 95th percentile.
[a]No data sets were identified in the SEMs, existing assessments, peer-reviewed literature search, or targeted search.

Indoor air concentrations were used to calculate exposures for two pathways: (i) inhalation of indoor air and (ii) dermal deposition from gas phase. Effectively, we assumed that the indoor air concentrations were all in gas phase because the absorption fraction of 1 was applied regardless of whether the chemical was in gas or particulate phase. With the exception of the two FTOHs, the indoor air concentrations were low for the other five targeted PFAS chemicals, with GMs ranging from <1 to 16 pg/m^3. Figure 6 presents the corresponding doses alongside those from other pathways, with panel (a) including background pathways and panels (b) and (c) excluding them. For PFOSA, PFBA, PFHpA, PFHxA, and PFBS, doses for indoor air inhalation ranged from approximately 10^{-10} to 10^{-8} mg/kg/day, while the doses for dermal deposition from gas phase were orders of magnitude lower, ranging from 10^{-12} to 10^{-14} mg/kg/day – both pathways had negligible contributions to the total exposure for these five PFAS chemicals. For 6:2 FTOH and 8:2 FTOH, for which indoor air concentrations were higher and dietary exposure (which was a primary contributor of exposure for the other PFAS chemicals) was zero, the inhalation pathway accounted for a significant portion of total exposure. Depending on the age group, inhalation of indoor air contributed 46% to 73% for 6:2 FTOH and 38% to 70% for 8:2 FTOH of total exposure, with doses ranging from 9.8×10^{-7} to 2.6×10^{-5} mg/kg/day. Dermal deposition from gas phase had a negligible contribution to total exposure, with doses in the 10^{-11} to 10^{-10} mg/kg/day range.

Similarly, indoor dust concentrations were also used to calculate exposures from two pathways: (i) ingestion of indoor dust and (ii) dermal absorption of dust. Indoor dust concentrations were higher than indoor air concentrations, with GMs ranging from approximately 4 to 72 ng/g for all PFAS chemicals; corresponding doses ranged from 9.6×10^{-10} to 3.2×10^{-7} mg/kg/day for indoor dust ingestion and from 7.3×10^{-10} to 2.3×10^{-6} mg/kg/day for dermal dust absorption. For 6:2 FTOH and 8:2 FTOH, indoor dust

ingestion accounted for approximately 2% to 6% of total exposure, while dermal dust absorption had higher contributions of 14% to 45% depending on the age group. For the remaining five PFAS chemicals, the indoor dust ingestion and dermal dust absorption doses accounted for <1% and <5%, respectively, of the total exposure.

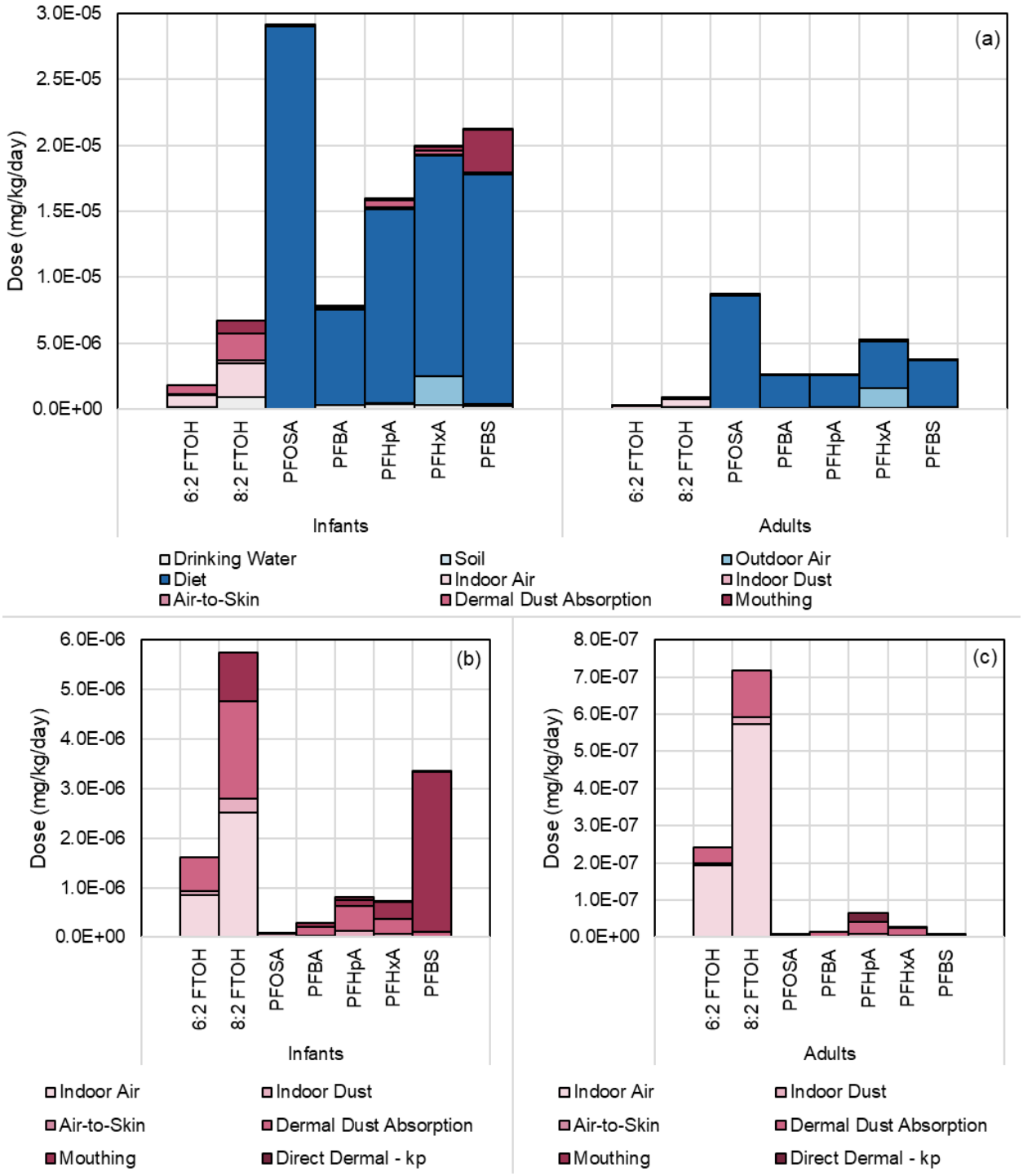

Figure 6. Estimated Exposure for Residential General Population Infants and Adults by Chemical and Pathway Based on Empirical Measurements (a) Including Background Exposure, (b) and (c) Excluding Background Exposure.

4.2.3.2. Direct Dermal Contact (from Wipe Data)

Adult skin wipe data were available from one study (Poothong et al., 2019) for PFHpA, PFHxA, and PFBS. For these three PFAS chemicals, the median reported concentration was below the method detection limit but the 75th percentile or maximum was a detectable value. All data were converted to units of mass per surface area sampled using the study-reported sampling area (i.e., both sides from the wrist to the fingertips, including the sides of the hand and the fingers) and recommended adult-specific body weights and surface area-to-body weight ratios (U.S. EPA, 2011). The study-reported mean and 95th percentile wipe concentrations were used to calculate the central tendency and high-end estimates of exposure. PFOSA was also measured in Poothong et al. (2019) but was not detected in any skin wipe sample.

Average daily dose from direct dermal exposure was calculated using the (i) fraction absorbed method and (ii) permeability coefficient method. Because data for other age groups was lacking, we used the dermal loading for adults, together with the recommended age group-specific body weights, to calculate dose for other ages. Similar to results reported in Liu et al. (2017) and in a previous call order under this contract for organohalogen flame retardants (Call Order No. 61320622F2012), higher doses were calculated using the permeability coefficient method compared to the fraction absorbed method (see Table 20), although the contribution to total exposure was <1%, as seen in Figure 6. In general, doses calculated using the fraction absorbed method were within one order of magnitude for the three chemicals with available data, while doses calculated using the permeability coefficient method were within two orders of magnitude.

Table 20. Study-Reported Mean Wipe Concentration and Corresponding Direct Dermal Dose for Adults Using the Fraction Absorbed and Permeability Coefficient Methods.

Chemical	Study-Reported Mean Wipe Concentration (ng)	Dose – Fraction Absorbed (mg/kg/day)	Dose – Permeability Coefficient (mg/kg/day)
PFHpA	0.13	4.91×10^{-10}	2.22×10^{-8}
PFHxA	0.05	2.39×10^{-10}	3.07×10^{-9}
PFBS	0.01	6.38×10^{-11}	2.60×10^{-10}

4.2.3.3. Mouthing

Two reports (Danish EPA, 2022; CEC, 2017) evaluated chemical migration rates from children's textiles to artificial saliva for various PFAS chemicals. In the Danish EPA study, migration tests were performed on eight products[2] that had been shown to have high

[2] The eight products tested in the Danish study were: snowsuit (n = 2), softshell suit (n = 1), infant sleeping bag (n = 1), rain jacket (n = 1), rain suit (n = 1), and mittens (n = 2).

concentrations of total fluorine and, upon further analysis, were shown to contain not just FTOHs but also other PFAS chemicals. Samples from each of the products were placed in artificial saliva at 37°C for 3 hours, without mixing, and the migration fluid at the end of the experiment was analyzed for PFAS content. The Commission for Environmental Cooperation (CEC) (2017) performed a similar migration experiment, wherein the items selected[3] were ones that previously showed total PFAS concentrations (sum of 31 PFAS chemicals analyzed) >0.5 ng/g. In contrast to the Danish study, in the CEC study the samples were placed in artificial saliva at 37°C, along with glass beads, and mechanically stirred for 1 hour using a rotational device (~30–40 rpm) to simulate friction.

The migration rates for individual products from the two studies are presented in Supplemental File F. The Danish study reported the migrated quantity (mass/area sampled), which we converted to migration rates by dividing by the duration of the experiment. For the CEC study, the concentration in saliva was reported in mass/mass units. We converted these values to migration rates using the surface area of the sample, the volume of artificial saliva, the density of saliva (1.036 g/mL), and the experimental duration.

Results from both studies showed that migration rates varied with product, with migration rates generally increasing with increasing product concentration. Only PFHxA and PFHpA had detectable migration rates from both studies. Because the products analyzed were different in the two studies, we compared the average migration rate across products with detectable concentrations, which showed that the migration rates from the CEC study were higher than those from the Danish EPA study (PFHxA: 1.10×10^{-2} versus 5.35×10^{-5} ng/cm^2/min; PFHpA: 2.84×10^{-3} versus 3.96×10^{-5} ng/cm^2/min) due to the mechanical stirring that would increase mass transfer. Given that the mechanical stirring more closely reflects the chewing and/or sucking action during mouthing, we used the migration rate data from the CEC study for PFHxA, PFHpA, PFBA, and PFBS. PFOSA was measured in both studies but was below the detection limit in the migration fluid for all products and therefore we set the migration rate to zero for PFOSA. Fluorotelomer alcohols were not target analytes in the CEC study due to their higher instrument detection limits compared to the other PFAS chemicals but 6:2 FTOH and 8:2 FTOH were evaluated in the Danish study, with seven of eight products showing detectable levels of 8:2 FTOH in the migration fluid at the end of the experiment. To account for the lack of mechanical stirring in the Danish study, we applied an adjustment factor of 200 (based on the difference in average migration rates between the two

[3] The items tested in the CEC study were children's rainsuit (n = 1), baby bib (n = 2), and a waterproof baby changing table mat (n = 1).

studies for PFHxA, which was more conservative than that for PFHpA) to the migration rates of individual products for 8:2 FTOH. No detectable levels of 6:2 FTOH were reported in the migration experiments and in the absence of data, we set the migration rate to zero.

For each chemical, we calculated GM using the individual product migration rates (after adjustment for 8:2 FTOH) and set the maximum rate as P95 (see Table 21). For PFBS, for which migration data were only available for one product (and therefore only one data point was available), we used the same migration rate for the GM and P95. Using daily mouthing durations of 70.1, 47.4, and 37 minutes for the <1 year-old, 1–2 year-old, and 3–5-year-old age groups (Greene, 2002), respectively, from a CPSC observational mouthing study and assuming a surface area mouthed of 10 cm^2, central tendency mouthing exposures were calculated and ranged from 2.2×10^{-8} to 3.2×10^{-6} mg/kg/day across all age groups and chemicals. For PFBA, PFHxA, and PFHpA, mouthing contributed <2% to total exposure, while for both 8:2 FTOH and PFBS, mouthing accounted for approximately 15%, 8%, and 6% of total exposure for the <1 year-old, 1–2 year-old, and 3–5-year-old age groups, respectively (see Figure 6).

Table 21. Migration Rates Used in Estimating Mouthing Exposure.

		Migration Rate ($ng/cm^2/min$)	
Chemical	n	GM	P95
8:2 FTOH[a]	7	1.09×10^{-2}	2.89×10^{-2}
PFBA	3	1.04×10^{-3}	5.99×10^{-3}
PFHpA	3	3.81×10^{-3}	2.99×10^{-2}
PFHxA	3	1.30×10^{-3}	6.91×10^{-3}
PFBS	1	3.57×10^{-2}	3.57×10^{-2}

n = number of products with detectable migration data; GM = geometric mean; P95 = 95th percentile.
[b]Migration rates from the study were adjusted using an adjustment factor of 200 to account for the lack of mechanical stirring in the CEC study.

4.2.3.4. Aggregate Total Exposures

Aggregate central tendency total exposures are presented in Figure 6 and ranged from 2.8×10^{-7} to 3.4×10^{-5} mg/kg/day across all chemicals and age groups. These doses include background exposures and use the direct dermal dose calculated with the permeability coefficient method to be conservative. With the exception of 6:2 and 8:2 FTOH, total exposure was predominantly due to background exposure, specifically dietary ingestion. For the two FTOHs, dietary exposure was zero and therefore total exposure was primarily due to inhalation of indoor air and dermal dust absorption, with mouthing also an important pathway for 8:2 FTOH.

4.2.3.5. Uncertainties and Limitations

Many of the uncertainties and limitations discussed for background exposures are also applicable for estimating doses from empirical measurements and are not discussed further in this section (see Section 4.2.1.2). In terms of data availability, data on personal dermal loading (wipe data) and migration rates from products into saliva were especially limited, with only one data set available for wipe data and two reports on migration data. For the migration rate data, limitations in the experimental design for one of the studies (i.e., lack of mechanical stirring) resulted in primarily only data from one study being used.

Many of the modeling equations used to estimate dose for the different pathways are widely accepted although exposure from the dermal absorption of dust pathway is typically not estimated because of the difficulty of quantification and its large interpersonal variability. The equations used in this report follow the approach from a previous call order under this contract (Call Order No. 61320622F2012) and required professional judgment to estimate the fraction of ingested dust due to hand-to-mouth transfer and the fraction of dust on hands that enter the mouth. We set these parameters to 0.75 and 0.05, respectively, and estimate these values to have an uncertainty factor of 2.

4.2.4. Exposures Estimated from Reverse Dosimetry

4.2.4.1. Pooled Whole Blood/Serum Concentrations and Corresponding Intakes

Thirty studies were identified across five PFAS chemicals (PFOSA, PFBA, PFHpA, PFHxA, PFBS) with concentrations in serum or whole blood. All serum data sets were converted to units of mass per volume using a density of 1.018 g/mL. Whole blood data sets were already in mass per volume units. Data sets were excluded if the central values were too small (represented as either <LOD or <0.08, for example) or for inconsistent order of statistics. Each data set was mapped to the closest age group, with umbilical cord data mapped to infants, and a normal distribution was fitted in log space. The fit was transformed back to regular space to determine the GM and GSD. A pooled GM was then calculated in log space for each age group, with the number of samples as the weighting factor.

Table 22 presents the pooled geometric mean and 95th percentile for blood/serum concentrations, with corresponding estimated daily intake doses presented in Figure 7 for infants and adults. Daily intakes across all chemicals were in the 10^{-6} to 10^{-4} mg/kg/day range, with the highest intake observed for PFBA and the lowest for PFHpA. Daily intakes were similar across the two age groups within a chemical. Limited data (i.e., one or two data sets) were also available for different age groups for PFHpA and PFBS and are available in Supplemental File G.

Table 22. Pooled Geometric Mean and 95th Percentile Whole Blood/Serum Concentration for Infants and Adults by Chemical.

		Whole Blood/Serum Concentrations (ng/mL)		
Chemical	Age Group	n	Pooled GM	Pooled P95
PFOSA	Infant	1	0.363	1.37
PFOSA	Adult	3	0.523	1.87
PFBA	Infant	4	2.80	7.18
PFBA	Adult	5	2.25	10.1
PFHpA	Infant	8	0.709	2.14
PFHpA	Adult	38	0.349	1.39
PFHxA	Infant	1	0.140	0.918
PFHxA	Adult	3	0.381	1.05
PFBS	Infant	7	2.18	5.29
PFBS	Adult	22	1.85	10.8

n = number of data sets; GM = geometric mean; P95 = 95th percentile.

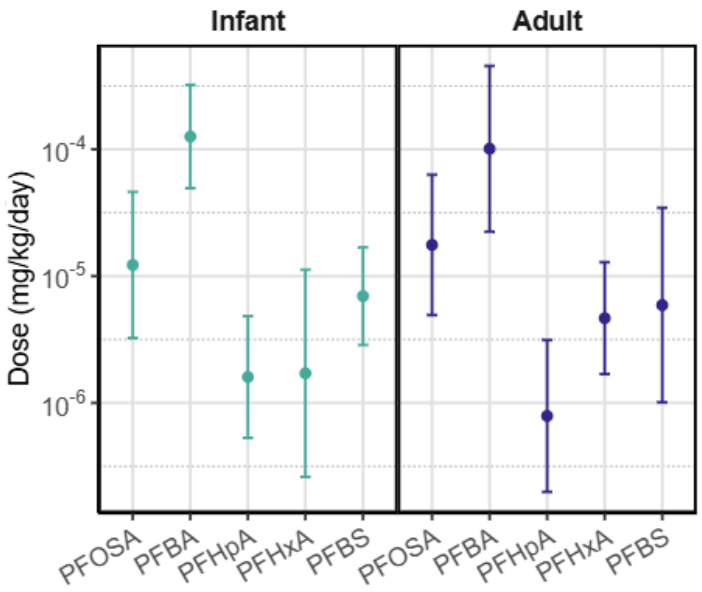

Figure 7. Estimated Daily Intake for Residential General Population Infants and Adults by Chemical Using Biomonitoring Data.

Geometric mean estimates; lower and upper whiskers represent the 5th and 95th percentiles, respectively.

4.2.4.2. Uncertainties and Limitations

The biomonitoring data used in this assessment were identified through a focused search and may not be representative of the full range of data available in the literature. Specifically, biomonitoring data were extracted from two existing assessments (ATSDR

2021, EFSA 2020) and one peer-reviewed article that summarized biomonitoring data (Liu et al., 2024b). In addition, individual cohort studies may not be nationally representative. Similarly, half-life values were also identified through a review of existing assessments. Given the limited data available for volume of distribution values, we used a single value of 0.202 L/kg for all chemicals, following the approach of Dawson et al. (2023), although volume of distributions may be dependent on the chemical. For example, in assessments of exposure to PFOA and PFOS, the volume of distribution was assumed to be 0.170 and 0.230 L/kg, respectively (Lorber and Egeghy, 2011; Egeghy and Lorber, 2011). Finally, while the simple one-compartment, first-order model applied at steady state is the most common toxicokinetic model used for PFAS chemicals (East et al., 2023), more complex models are emerging that may be more appropriate depending on the chemical.

4.2.5. Comparison of Estimated Exposures from Different Approaches

Figure 8 compares the doses estimated from the three approaches. Doses calculated from human biomonitoring data represent exposures from all sources and pathways to which a person is exposed and should theoretically be higher than doses calculated from mechanistic models and empirical measurements. In general, for the five targeted PFAS chemicals with biomonitoring data (PFOSA, PFBA, PFHpA, PFHxA, PFBS), doses estimated from the SHEDS-HT model were the highest, followed by doses calculated from empirical measurements, and finally doses estimated using biomonitoring data. As discussed in Section 4.2.2.4, the higher SHEDS-HT doses are likely overestimates of exposure because of the input parameters used, wherein we purposefully set the chemical prevalence to 1 and computed summary statistics on the subpopulation of simulated individuals with non-zero exposures. Even with this overestimation for SHEDS-HT, the central tendency doses for the three approaches were roughly within two orders of magnitude of each other. For 6:2 and 8:2 FTOH, for which doses were estimated using SHEDS-HT and empirical measurements, the doses from the two approaches were within two to three orders of magnitude of each other. No empirical measurements or biomonitoring data were available for DFE or TFE and therefore exposure was only estimated using SHEDS-HT. However, as seen in Figure 8, the uncertainty in the estimated exposure is large, with the whiskers for the 5th and 95th percentiles spanning several orders of magnitude. Doses estimated from biomonitoring data were generally consistent with doses estimated from empirical measurements, with the two estimates within approximately one order of magnitude of each other. With more realistic values for the two key SHEDS-HT assumptions (the chemical prevalence of 1 and removal of nonusers), the doses estimated with SHEDS-HT and empirical measurements should be within the uncertainty range of each other.

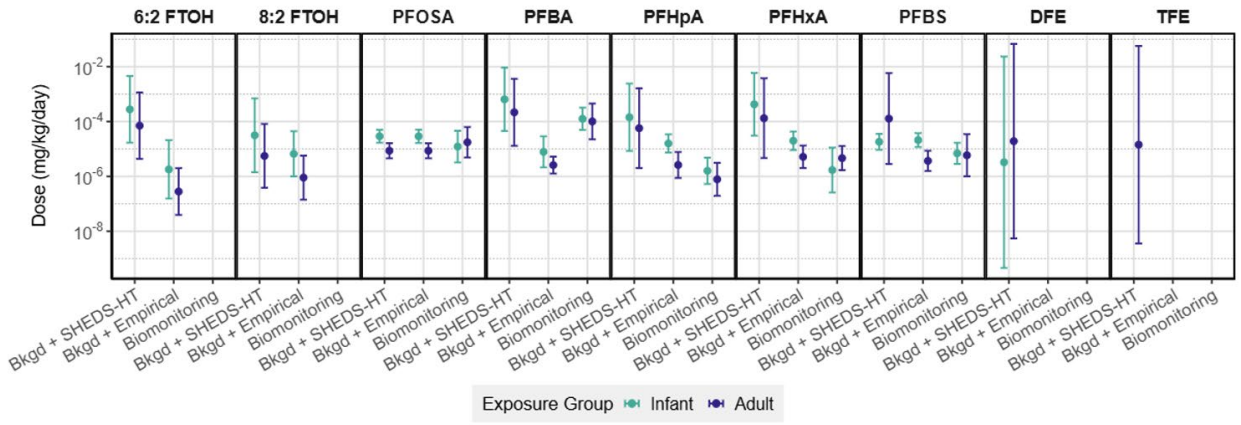

Figure 8. Comparison of Doses Calculated from Individual Exposure Assessment Approaches.

Geometric mean estimates; lower and upper whiskers represent the 5th and 95th percentiles, respectively.

4.3. Risk

4.3.1. Risk Characterization

To perform a probabilistic screening-level risk assessment based on the exposure and TRV distributions, the distributions for exposure and TRV were divided as described in Section 3.4 to produce HQs for each chemical. From the HQ distribution, the probabilities and resulting cumulative probability (Pr) distribution were calculated to identify the proportion of the population that was potentially exposed above the TRV.

During a traditional risk assessment, a single HQ is calculated by dividing the mean or median exposure level by the TRV and an HQ > 1 is thought to represent the level at which sensitive populations may begin to experience mild effects. As such, one interpretation of Pr(HQ > 1) is that (at relatively low probabilities) it represents the probability of a member of the population developing effects based on the given exposure scenario. Consistent with the approach developed in a previous call order under this contract (Call Order No. 61320623F2030) and on the work presented in Chiu and Slob (2015), we considered Pr values above 0.10 (i.e., more than 10%, or more than 10 of 100) to be higher probability of chronic risk to human health.

Figure 9 presents the Pr(HQ > 1) for infants and adults using each of the three different approaches to estimate exposure (see Supplemental File H for values). Importantly, exposure estimates, and thus risk values, were not developed using empirical measurements or biomonitoring data for DFE or TFE because no such data were available. There were also no TFE exposure estimates for infants using SHEDS-HT because infants did not use any products containing TFE. Additionally, biomonitoring data were not

available for 6:2 FTOH and 8:2 FTOH as these chemicals rapidly biotransform into other PFAS chemicals and therefore no risk values were calculated.

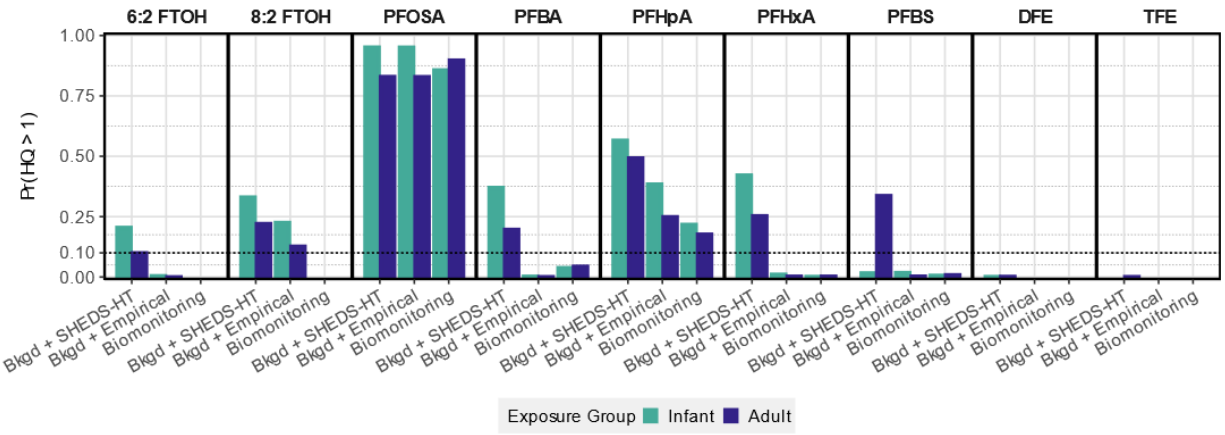

Figure 9. Cumulative Probability of the Hazard Quotient Being Greater Than 1.

For each chemical, six Pr(HQ > 1) values were calculated, one for each of the three exposure estimation approaches (i.e., SHEDS-HT, empirical measurements, and biomonitoring for both infants and adults) used for the two populations (i.e., infants and adults). Using the 0.1 threshold for the Pr(HQ > 1) values, we identified three groups of chemicals:

- Those of highest probability for potential chronic risk to human health were chemicals for which at least four of the six Pr(HQ > 1) values were ≥0.1.
- Those of high probability for potential chronic risk to human health were chemicals for which one to three of the six Pr(HQ > 1) values were ≥0.1.
- Those of low probability for potential chronic risk to human health were chemicals for which none of the six Pr(HQ > 1) values were ≥0.1.

For each group of chemicals, we examined the relationship between the developed TRV and exposure distributions. The probability density distributions for the TRV and estimated exposures are shown below for each chemical, arranged by the degree of probability of risk observed.

4.3.2. Chemicals of Highest Probability for Chronic Risk

Three chemicals (8:2 FTOH, PFOSA, and PFHpA) were identified to be chemicals of highest probability for chronic risk. For these chemicals, Figure 10 shows that generally there is close to 100% overlap of the exposure estimate distributions against the TRV distributions. Additionally, when compared to the corresponding exposure distributions, the TRV distributions for these chemicals generally have greater variability, indicating

potential uncertainty in the estimate of the TRV, suggesting uncertainty in the derived Pr value, which could be mitigated as more chemical-specific information is used to update the TRV. However, for PFOSA, the central tendency of the estimate of the TRV is less than the central tendencies of exposure estimated from the different approaches. As such, the uncertainty of the TRV for PFOSA may have less influence on the uncertainty of the Pr value.

Also of note for PFOSA is the almost complete overlap in distributions between exposures estimated using SHEDS-HT and exposures estimated using empirical measurements. While exposure estimates from SHEDS-HT and empirical measurements are generally higher than those estimated from biomonitoring data for infants, there is an inverse relationship for adults, with the estimates from SHEDS-HT and empirical measurements generally lower than those from biomonitoring data. Despite these findings for PFOSA, it is important to emphasize that limited data were identified for the exposure assessment and therefore exposure estimates for PFOSA should be interpreted with caution. This, coupled with the lower estimate of central tendency for the TRV, suggests that it may be of greatest value to develop more chemical-specific information for PFOSA given that exposure appears to be closer to the higher side of the hazard estimate. For both 8:2 FTOH and PFHpA, the development of more chemical-specific data would improve hazard quantification as well and would be more necessary to determine whether more regulation is needed as the trend of central tendencies is less clear.

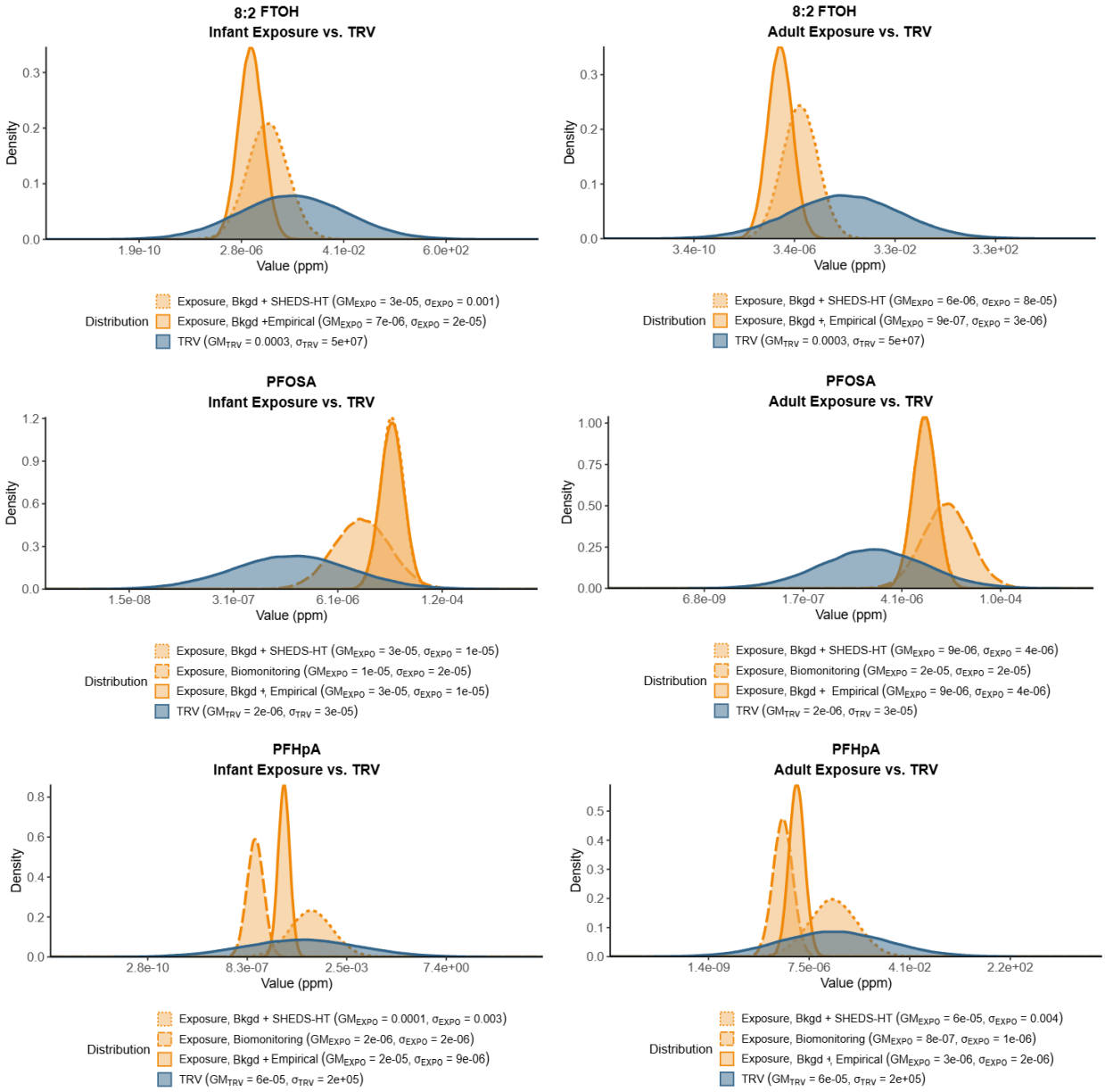

Figure 10. Exposure and TRV Distributions for Chemicals with Highest Probability for Chronic Risk.

4.3.3. Chemicals of High Probability for Chronic Risk

Four chemicals (6:2 FTOH, PFBA, PFHxA, and PFBS) were identified as chemicals of high probability for chronic risk. For all four chemicals, Figure 11 shows that the central tendency of the TRV appears to be higher than the central tendency of the exposure estimates, regardless of the exposure estimation approach used, suggesting that only a selection of the population is exposed to levels at which health effects may begin to emerge. In this group of chemicals, there also appears to be marked differences in the exposure estimates depending on the approach used, leading to large differences with the risk estimates. Examples of differences in exposure estimates are seen in PFBA in

particular. Specifically, for both infants and adults, the distributions from each exposure estimation approach are distinct, with differences apparent in the central tendency and spread. For the other three chemicals, differences in exposure estimates depending on the approach used are also apparent and are propagated through to the estimates of risk displayed in Figure 9.

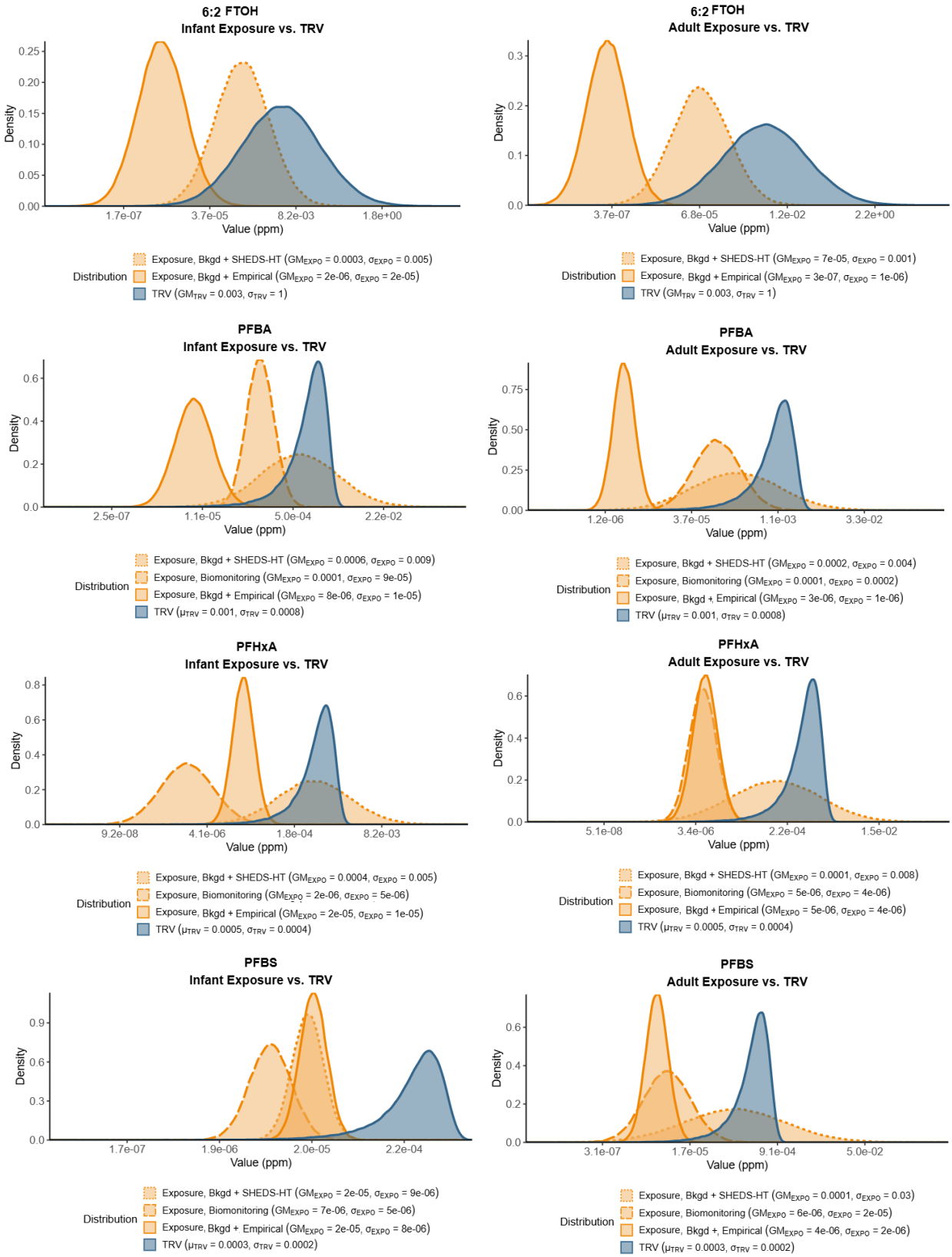

Figure 11. Exposure and TRV Distributions for Chemicals with High Probability for Chronic Risk.

4.3.4. Chemicals with Low Probability for Chronic Risk

Two chemicals (DFE and TFE) were identified as chemicals with low probability for chronic risk. Note this classification is based on chronic exposure scenarios, with a discussion of acute exposures and corresponding hazards and risks associated with huffing discussed in Supplemental File B. Acute risks are probable based on comparison of estimated exposures and acute TRVs for both chemicals.

Generally, for chemicals with low probability for chronic risk, Figure 12 shows that there is no/minimal overlap between the exposure and TRV distributions, with SHEDS-HT the only approach used to estimate exposure. While exposures could not be calculated using the other two approaches due to a lack of empirical measurements and biomonitoring data, the comparison of exposure results across the three approaches in Section 4.2.5 showed that SHEDS-HT provides the most conservative estimate of exposure for the other chemicals. As such, although these chemicals do suffer from more limited exposure data, generally, based on the differences in the TRV and SHEDS-HT exposure distributions, they have a low probability for chronic risk. No data are presented for infants exposed to TFE because infants did not use any products containing TFE and therefore there were no estimated exposures.

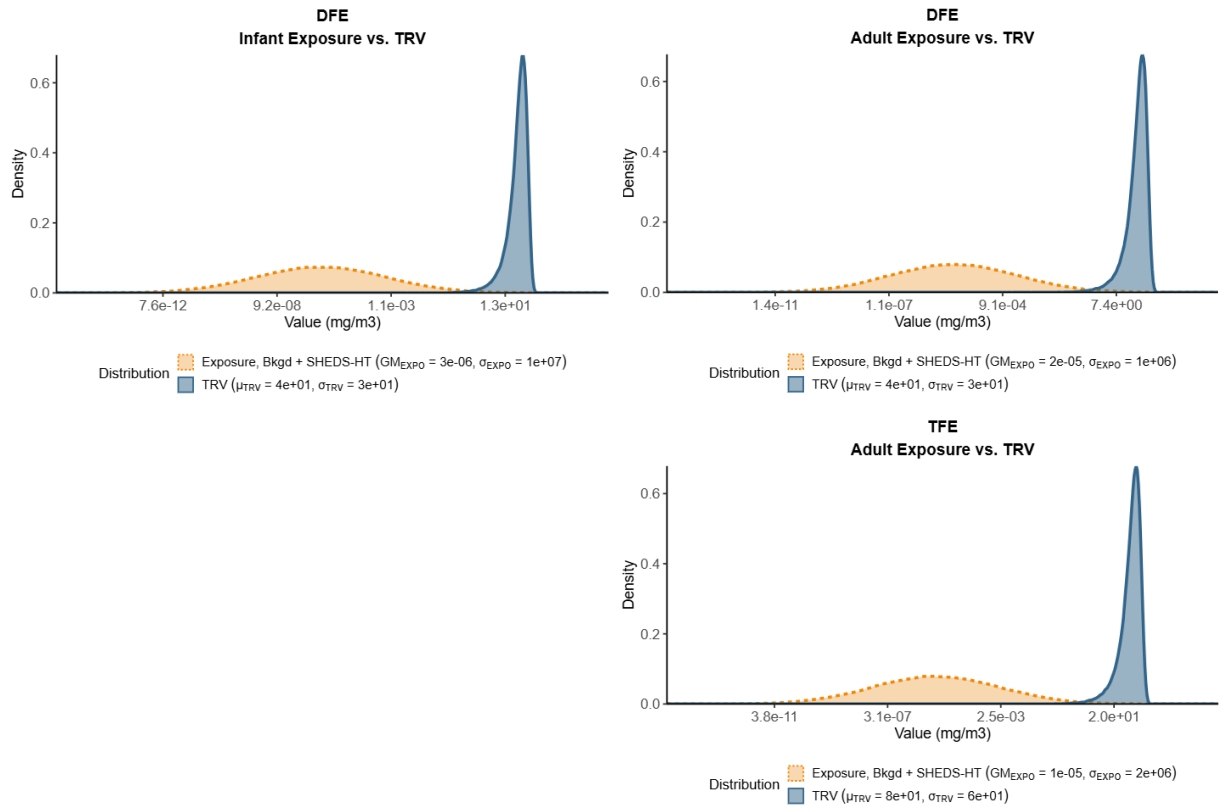

Figure 12. Exposure and TRV Distributions for Chemicals with Low Probability for Chronic Risk

4.3.5. Uncertainties and Limitations

While the risk estimates are fairly well characterized, it is important to note that the choices made during the assessment, particularly related to hazard, do represent some limitations of the approach. Specifically, in the application of uncertainty factors to derive TRVs and in the bounding of the TRV distribution, more nuanced considerations should be given to those estimates that rely on larger uncertainty factors, such as those presented in Section 4.3.2 (Dourson et al., 1996). Specifically, additional toxicity or exposure data could be gathered or generated for 8:2 FTOH, PFOSA, and PFHpA based on the higher values for Pr(HQ > 1). Although the estimates for these chemicals are quite high, the developed method does not reflect the entire population of the United States and instead represents a smaller subpopulation using consumer products containing these chemicals. Narrowing the TRV estimate will result in a more accurate estimate of the actual proportion of the population exposed to a level at which health effects may begin to emerge.

Related to the idea of bounding of the distribution, other options exist for bounding these estimates, such as using different agency TRVs, rather than just the values from the EPA, or different factors to establish the confidence limits. However, given the limited chemical database, this option was not ideal. Also, importantly, even those TRVs that came from authoritative sources were based on limited databases, particularly with respect to species (i.e., only rats and mice), exposure durations, and endpoints that have been studied.

The TRV distributions were compared to distributions of exposure that were estimated using three different approaches. As previously discussed in Section 4.2, several chemical-media combinations had limited data available and therefore some exposure estimates were made based on surrogate concentrations (e.g., use of drinking water LODs for 6:2 FTOH and 8:2 FTOH) or use of one data set (e.g., skin wipe data), leading to uncertainties in the estimates of exposure. For modeled estimates of exposure using SHEDS-HT, the choice of input parameters and postprocessing approach can have an effect on the resulting exposures, as discussed in Section 4.2.2.4. As previously noted, some exposure estimates only existed for one population (e.g., only for adults, not infants), particularly in the "chemicals with low probability for chronic risk" group, DFE and TFE. Additionally, exposures can change over time and should exposures increase in the future, the probability of chronic risk would increase.

4.4. Ammonium Perfluorooctanoate

The previous sections present screening-level estimates of hazard, exposure, and risk for nine PFAS chemicals. A tenth chemical, APFO, was also initially selected for evaluation to

represent a PFAS salt. PFAS salts are formed when the acid form of a PFAS chemical reacts with a base to form the salt (e.g., perfluorooctanoic acid reacts with ammonia to form APFO). Because they dissociate to the anion, PFAS salts represent a potential source of PFAS chemicals in consumer products. Specifically for APFO, Vierke et al. (2012) noted that with the acid dissociation constant (pKa) reported in the literature as -0.2 to 3.8, more than 99% of APFO is present as perfluorooctanoate at normal environmental conditions (i.e., pH 7) and in general, perfluorooctanoate is the form measured in environmental and human samples although studies may report the measured values as PFOA or APFO.

In terms of hazard, the EPA's (2024a) *Final Human Health Toxicity Assessment for Perfluorooctanoic Acid (PFOA) and Related Salts* included non-metal salts of PFOA, such as APFO, and therefore the final toxicity values for PFOA are applicable to APFO (i.e., chronic oral RfD of 3×10^{-8} mg/kg/day, oral cancer slope factor of 0.0293 $(ng/kg/day)^{-1}$). To assess exposure, previous efforts (see Supplemental File A) identified the CPSC white paper *Characterizing PFAS Chemistries, Sources, Uses, and Regulatory Trends in U.S. and International Markets* (RTI, 2023) as having information on known or potential uses of APFO in consumer products. However, during the preparation of this report, we could not identify specific consumer products with APFO. Specifically, the products listed in the white paper were coatings in general; plastics, resins, and rubber; general use – automotive; and mold release agent in general (products related to food contact materials were not included as food contact materials are outside the jurisdiction of CPSC). These product descriptions were too broad to determine where APFO would be found and a backward search of the original source(s) did not provide additional detail. Several sources indicated that APFO has been used for decades as a processing aid in the polymerization of fluoropolymers (Washburn et al. 2005; Gluge et al. 2020; Gaines et al. 2022), with Washburn et al. (2005) noting that residual perfluorooctanoate may be present in fluoropolymer films and membranes used to manufacture certain consumer products; however, specific examples of consumer products were not provided. In the absence of consumer product information, we were not able to model exposure using SHEDS-HT. Only mechanistic modeling was considered for estimating exposure. Because APFO rapidly dissociates to perfluorooctanoate and concentrations of perfluorooctanoate in environmental media or human biomatrices could be due to multiple sources (e.g., PFOA, metal salts), doses estimated using empirical measurements or biomonitoring data would not reflect only APFO exposure. In the absence of an estimate of exposure, risk was not characterized for APFO.

5. Summary

We performed a screening-level risk assessment on nine PFAS chemicals to determine potential risk to human health. A tenth chemical was also initially selected for evaluation to represent a PFAS salt but was ultimately not pursued because an exposure assessment could not be conducted because of a lack of consumer product information.

In this report, we present a probabilistic approach to risk assessment, which was developed in a previous call order under this contract (Call Order No. 61320623F2030). We performed gray and peer-reviewed literature searches to identify data related to both hazard and exposure. For hazard, these data were reviewed to identify TRVs from authoritative sources when they existed (five chemicals). When no authoritative TRVs were identified, candidate TRV derivation and selection was performed when possible (two chemicals) and TRV distributions were parameterized when no chemical-specific information existed (two chemicals). For exposure, empirical measurements in environmental media, biomonitoring data, and product concentration data were identified from the literature, primarily from review articles or authoritative assessments, and were used to estimate exposure for different age groups. To calculate risk, the TRVs and exposure estimates from the previous steps were used to parameterize TRV and exposure distributions. The exposure and hazard distributions were then divided (for log normal distributions of TRV) or sampled (for normal distributions of TRV) to develop risk estimates using an HQ analysis.

From our risk characterization step, we identified three chemicals that have the highest probability for chronic risk to human health (8:2 FTOH, PFOSA, and PFHpA), four chemicals with high probability for chronic risk to human health (6:2 FTOH, PFBA, PFHxA, and PFBS), and two chemicals with low probability for chronic risk to human health (DFE and TFE) in accordance with how consistently different exposure estimates resulted in a Pr (HQ>1)>0.1. These results suggest prioritizing the gathering of chemical-specific data particularly for PFHpA, PFOSA, and 8:2 FTOH, which are the chemicals with the most uncertainty in the TRV estimate. PFOSA, in particular, has a current central tendency estimate for the TRV that is lower than any of the estimated exposure values and would therefore benefit from additional hazard investigation. In addition, the limited amount of identified exposure data for PFOSA suggests that exposure estimates can be refined with additional sources of data.

The key limitations of this assessment are in the chemical database uncertainty for hazard and the paucity of data for certain pathways of exposure. Specifically related to the database, for those chemicals for which chemical-specific data were most sparse (PFHpA and PFOSA), we relied on read-across extrapolations from chemicals similar to

the targeted PFAS chemicals, which may over- or underestimate toxicity. For those chemicals for which more recent data did exist (8:2 FTOH and 6:2 FTOH) as well as for those with authoritative assessments (PFBA, PFHxA, PFBS, DFE, and TFE), there were still limitations on the data. Specifically, these chemicals only had rodent assessments, no chronic exposure assessments, and a limited number of endpoints. Given that PFAS as a class have species-specific differences in mechanisms of action, and toxicokinetic factors may significantly affect the potency of these chemicals, the lack of these data is of particular concern. Importantly, while many of these PFAS chemicals have been evaluated for a variety of health outcomes in epidemiologic studies (except for the FTOHs), evidence is still limited for the targeted chemicals with outcomes commonly observed in animals such as hepatic, endocrine, renal, and developmental effects. This lack of evidence makes it difficult to draw conclusions about the human relevance of significant findings in animals.

In terms of exposure, three approaches were used to estimate exposure, with two relying on measured data (i.e., empirical measurements or biomonitoring data) and one relying on modeled estimates (i.e., SHEDS-HT). For estimates derived from measured data, certain chemical-media combinations had fewer than five data sets identified, leading to greater uncertainty in the estimates. Modeled estimates were generally higher than those from the other two approaches because we purposefully set the chemical prevalence to 1 and computed summary statistics only for the subpopulation of simulated individuals with non-zero exposures. These inputs can be refined with updated consumer surveys, which would lead to more refined values.

Overall, future investigation could include derivation and compilation of more chemical-specific data for this targeted subset of PFAS chemicals, for the reasons highlighted above, in addition to mixtures assessment of these PFAS chemicals as humans are exposed to complex PFAS mixtures. Our assessment evaluated each chemical independently (i.e., single-chemical assessment), but there may be synergistic effects between some of the targeted chemicals or with other PFAS chemicals that are not quantitatively accounted for with the TRVs estimated in this assessment. A mixtures assessment would provide more detailed information about risk that would complement the single-chemical assessments described here.

Additionally, this analysis focused on 10 prioritized PFAS chemicals. There are a few dozen more PFAS chemicals that currently have enough information to proceed with an analysis similar to the one in this report. There are also several hundred more PFAS substances that are currently used in commerce but do not yet have enough information to proceed with such an analysis. This process could be repeated for additional PFAS chemicals to

identify exposure and hazard patterns that could inform a future risk assessment based on PFAS subclasses.

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7. Supplemental Files

Table 23. List of 30 Supplemental Files.

Filename Prefix Category	Filename(s)	Description
Supplemental File A (1 file)	Supplemental File A_PFAS Prioritization Approach_2025-05-23.docx	Description and results of prioritization approach used to determine a set of prioritized PFAS chemicals
Supplemental File B (6 files)	Supplemental File B_Huffing Scenario_2025-06-23.docx Attachment B-01_DFE 6 hrs Huffing Results_2025-05-23.xlxs Attachment B-02_DFE 2 hrs Huffing Results_2025-05-23.xlxs	Discussion of hazards, exposures, and risks for acute exposures associated with huffing

Filename Prefix Category	Filename(s)	Description
	Attachment B-03_TFE 6 hrs Huffing Results_2025-05-23.xlxs Attachment B-04_TFE 2 hrs Huffing Results_2025-05-23.xlxs Attachment B-05_CEM Postprocessing for Huffing_2025-05.23.R	
Supplemental File C (1 file)	Supplemental File C_Literature Search and Screening_2025-05-23.xlxs	Literature search terms and PECO criteria
Supplemental File D (1 file)	Supplemental File D_TRVs for Prioritized PFAS_2025-05-23.xlsx	TRV extractions and derivations
Supplemental File E (17 files)	Supplemental File E_SHEDS-HT_2025-06-10.docx Attachment E-01_chem_props_pfas_2025-05-23.csv Attachment E-02_source_chem_pfas_2025-05-23.csv Attachment E-03_source_vars_pfas_2025-05-23.csv Attachment E-04_source_scen_pfas_2025-05-23.csv Attachment E-05_6-2 FTOH_SHEDS-HT Results_2025-05-23.xlsx Attachment E-06_8-2 FTOH_SHEDS-HT Results_2025-05-23.xlsx Attachment E-07_PFOSA_SHEDS-HT Results_2025-05-23.xlsx Attachment E-08_PFBA_SHEDS-HT Results_2025-05-23.xlsx Attachment E-09_PFHpA_SHEDS-HT Results_2025-05-23.xlsx Attachment E-10_PFHxA_SHEDS-HT Results_2025-05-23.xlsx Attachment E-11_PFBS_SHEDS-HT Results_2025-05-23.xlsx Attachment E-12_DFE_SHEDS-HT Results_2025-05-23.xlsx Attachment E-13_TFE_SHEDS-HT Results_2025-05-23.xlsx Attachment E-14_Postprocessed SHEDS-HT Results_2025-05-23.xlsx Attachment E-15_SHEDS-HT Postprocessing_2025-05-23.R Attachment E-16_Database_Fitting_2025-05-23.R	Exposures calculated using SHEDS-HT (Attachment E-16_Database_Fitting_2025-05-23.R is also used to fit data and calculate exposures estimated using empirical data and biomonitoring data)
Supplemental File F (1 file)	Supplemental File F_Empirical Measurements Data_2025-06-10.xlsx	Exposures calculated using empirical measurements, including for background exposure

Filename Prefix Category	Filename(s)	Description
Supplemental File G (1 file)	Supplemental File G_Biomonitoring Data_2025-06-10.xlsx	Exposures calculated using biomonitoring data
Supplemental File H (2 files)	Supplemental File H_Risk Characterization_2025-05-27.xlsx Attachment H-01_Cumulative Probability_2025-05-27.R	Risk values