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ORD Human Health Toxicity Value for Perfluoropropanoic Acid

(CASRN 422-64-0 | DTXSID8059970)

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Cincinnati, OH 45268

DISCLAIMERS

This human health assessment was developed by EPA's Office of Research and Development (ORD) to respond to a request from the EPA Office of Enforcement and Compliance Assurance (OECA), in support of site-specific decision-making under the purview of the Safe Drinking Water Act. This document has been reviewed in accordance with EPA policy and approved for publication. This human health assessment has received internal peer review by at least two EPA/ORD/CPHEA scientists and an independent, external peer review by at least three scientific experts outside of EPA. All users should consider the information provided in this document to ensure that the toxicity value(s) are appropriate for the decision-context. Questions regarding the content of this assessment should be directed to the U.S. EPA website at https://ecomments.epa.gov/risk.

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AUTHORS, CONTRIBUTORS, AND REVIEWERS

Chemical Managers/Authors

Jason C. Lambert, PhD, DABT	U.S. EPA, Center for Computational Toxicology and Exposure
Lucina Lizarraga, PhD	U.S. EPA, Center for Public Health and Environmental Assessment
Elizabeth Oesterling Owens, PhD	U.S. EPA, Center for Public Health and Environmental Assessment

Contributors

Avanti Shirke, MPH	U.S. EPA, Center for Public Health and Environmental Assessment
Christine Cai, MS	
Elizabeth G. Radke, PhD	

Production Support

Dahnish Shams Jessica Soto-Hernandez Ryan Jones Samuel Thacker Vicki Soto	U.S. EPA, Center for Public Health and Environmental Assessment
Lauren Johnson	Student Services Contractor, Oak Ridge Associated Universities (ORAU)

Primary Internal Reviewers

Andrew Kraft, PhD	U.S. EPA, Center for Public Health and Environmental Assessment
J. Allen Davis, MSPH	

Primary External Reviewers[1]

Gloria B. Post, PhD, DABT	New Jersey Department of Environmental Protection
Panagiotis G. Georgopoulos, PhD	Rutgers University
Penelope A. Rice, PhD, DABT	U.S. Food and Drug Administration

Executive Direction

Wayne Cascio, MD	CPHEA Center Director
V. Kay Holt	CPHEA Deputy Center Director
Samantha Jones, PhD	CPHEA Associate Director
Kristina Thayer, PhD	CPHEA Chemical and Pollutant Assessment Division Director

Questions regarding the content of this assessment should be directed to the EPA Office of Research and Development (ORD) Center for Public Health and Environmental Assessment (CPHEA) website at https://ecomments.epa.gov/.

[1] Dr. Post and Dr. Rice conducted this review as independent consultants and not as a representative of the New Jersey Department of Environmental Protection and the U.S. Food and Drug Administration, respectively.

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COMMONLY USED ABBREVIATIONS AND ACRONYMS

AIC	Akaike's information criterion
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMCL	benchmark concentration lower confidence limit
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDS	Benchmark Dose Software
BMR	benchmark response
BW	body weight
CASRN	Chemical Abstracts Service registry number
CBI	nonconfidential business information
CERI	Chemicals Evaluation and Research Institute
CPHEA	Center for Public Health and Environmental Assessment
DTXSID	DSSTox substance identifier
EPA	Environmental Protection Agency
FT3	free triiodothyronine
FT4	free thyroxine
GGT	γ-glutamyl transferase
GLP	Good Laboratory Practice
HbA1c	form of hemoglobin linked to sugar
HED	human equivalent dose
HERO	Health and Environmental Research Online
IRIS	Integrated Risk Information System
LOAEL	lowest-observed-adverse-effect level
NLM	National Library of Medicine
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
OECD	Organization for Economic Cooperation and Development
ORD	Office of Research and Development
PBPK	physiologically based pharmacokinetic
PECO	populations, exposures, comparators, and outcomes
PFAS	per- and polyfluoroalkyl substances
PFOA	perfluorooctanoic acid
PFOS	perfluorooctane sulfonic acid
PFPrA	perfluoropropanoic acid
POD	point of departure
POD_{HED}	human equivalent POD
QA	quality assurance
RD	relative deviation
RfC	inhalation reference concentration
RfD	oral reference dose
SD	standard deviation
TGAb	thyroglobulin antibody
TIAB	title or abstract
TMAb	thyroid microsomal antibody
TSH	thyroid stimulating hormone
UF	uncertainty factor
UF_A	interspecies uncertainty factor
UF_C	composite uncertainty factor
UF_D	database uncertainty factor
UF_H	intraspecies uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
U.S.	United States of America
WoS	Web of Science

BACKGROUND

The U.S. Environmental Protection Agency (EPA) Office of Research and Development (ORD) under the Health and Environmental Risk Assessment National Research Program has developed a human health toxicity value for perfluoropropanoic acid (PFPrA; Chemical Abstract Services Registry Number [CASRN 422-64-0]). The assessment was developed in response to a request for site-specific technical support and scoped to help meet site-specific public health goals. The assessment provides qualitative and quantitative toxicity information that can be used, along with exposure information and other important considerations, to assess potential health risks to determine if, and when, taking action to address this chemical is appropriate.

The express purpose of this assessment is to provide support for risk-based decision-making pertaining to chronic exposures to PFPrA at sites or geographic locations or in specified environmental media (e.g., water, soil, air). Several factors are considered during scoping and problem formulation activities to ensure the assessment appropriately fits the intended purpose. These factors include the anticipated end-user need, peer-review and public comment requirements, and anticipated availability of hazard and dose-response evidence. Factors are assessed and informed through direct conversations with the requesting office(s) (e.g., EPA/OECA).

Noncancer and cancer toxicity values are derived (when supported by data) after a systematic review of the relevant scientific literature, an evaluation of available hazard and dose-response information using established EPA guidelines on human health risk assessment, and appropriate internal EPA and external independent peer reviews. To the extent possible based on the currently available evidence, the objective of this assessment is to present the major conclusions reached in the hazard identification and derivation of human health toxicity values and to characterize the overall confidence in these conclusions and values. This assessment is not intended to represent a comprehensive treatise on the chemical. For example, less emphasis is placed on providing definitive judgments of the integrated weight of evidence.

PFPrA Quality Assurance

This work was conducted under the EPA Quality Program to ensure data are of known and acceptable quality to support their intended use. Surveillance of the work by the assessment managers and programmatic scientific leads ensured adherence to quality assurance (QA) processes and criteria and to quick and effective resolution of any problems. The QA manager, assessment managers, and programmatic scientific leads have determined this work meets all EPA quality requirements. This human health assessment was written with guidance from the Center for Public Health and Environmental Assessment (CPHEA) Program Quality Assurance Project Plan, the Quality Assurance Project Plan titled *Umbrella Quality Assurance Project Plan for CPHEA Fit-For-Purpose Toxicity Assessments (L-CPAD-0033369-QP-1-2),* and the contractor-led *Quality Assurance Project Plan, General Support of CPHEA Assessment Activities (L-CPAD-0031961-QP-1-2)*. As part of the QA system, a quality product review is completed prior to management clearance. During assessment development, a Technical Systems Audit was performed on December 15, 2022, with no major findings.

This assessment received internal peer review by two EPA/ORD/CPHEA scientists and an independent, external peer review by three scientific experts outside of EPA. External peer review was managed by Eastern Research Group, Inc. (110 Hartwell Avenue Lexington, MA 02421) under contract EP-C-17-017. The reviews focused on whether studies were correctly selected and interpreted and adequately described for the purposes of this ORD assessment. The reviews also covered quantitative and qualitative aspects of the toxicity value development and addressed whether uncertainties associated with the assessment were adequately characterized.

INTRODUCTION

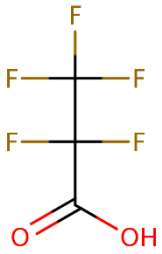
Per- and polyfluoroalkyl substances (PFAS) are a large group of anthropogenic chemicals that include the well-known C8 species, perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), and thousands of other structurally diverse fluorinated species. The universe of environmentally relevant PFAS, including parent chemicals, metabolites, and abiotic degradants, includes more than 12,000 substances.[2]

PFAS have strong, stable carbon-fluorine (C-F) bonds, making them resistant to hydrolysis, photolysis, microbial degradation, and metabolism (Ahrens, 2011; Buck et al., 2011; Beach et al., 2006). The chemical structures of PFAS make them repel water and oil, remain chemically and thermally stable, and exhibit surfactant properties. These properties make PFAS useful for commercial and industrial applications and purposes but also make some PFAS persistent in the human body and the environment (Calafat et al., 2019; Calafat et al., 2007). Due to their widespread use, physicochemical properties, persistence, mobility, and bioaccumulation potential, many PFAS occur in exposure media (e.g., air, water, ice, sediment) and in tissues and blood of aquatic and terrestrial organisms and humans.

Humans are widely exposed to PFAS (Sunderland et al., 2019), and PFAS have been shown to pose ecological and human health hazards (Fenton et al., 2021; U.S. EPA, 2021c, d; DeWitt, 2015; Hekster et al., 2003). The available toxicity data, however, are limited to relatively few, well-studied PFAS (e.g., PFOA, PFOS, GenX chemicals, PFBS and others). Most of the PFAS structures listed in EPA's CompTox Chemicals Dashboard[1] are data poor, having little to no toxicity data that might inform potential hazards to human health. One of these PFAS, PFPrA (CASRN 422-64-0), has been detected in surface and ground waters in or around manufacturing facilities. PFPrA, and its related salts, are all members of the overall PFAS class. This assessment applies to the desalted acid form of PFPrA as well as salts (including non-metal or alkali metal salts) of PFPrA that would be expected to fully dissociate in aqueous solutions of pH ranging from 4-9 (e.g., in the human body). The synthesis of evidence and toxicity value derivation presented in this assessment focuses on the forms of PFPrA with currently available toxicity data. PFPrA is a short-chain, three-carbon perfluoroalkyl carboxylic acid and is a clear and colorless liquid. The molecular formula and experimental or predicted physicochemical properties of PFPrA are presented in Table 1.

[2]https://comptox.epa.gov/dashboard/chemical_lists/PFASMASTER.

Table 1. Physical and Chemical Properties of PFPrA

Property or Endpoint (unit)	Value	Reference
Structure		U.S. EPA (2021a)
CASRN	422-64-0	
DTXSID	8059970	
Synonyms	Perfluoropropanoic acid Pentafluoropropanoic acid Propanoic acid, 2,2,3,3,3-pentafluoro Propanoic acid, pentafluoro- Propionic acid, pentafluoro- 2,2,3,3,3-Pentafluoropropanoic acid 2,2,3,3,3-Pentafluoropropionic acid Pentafluoropropionic acid ácido pentafluoropropionico Pentafluorpropionsaure Acide pentafluoropropionique PFPA PFPrA	
Molecular formula	$C_3HF_5O_2$	
Molecular wt. (g/mol)	164.031	
Physical description	Liquid, clear and colorless	CERI (2002c)
Odor	NA	
Melting pt. (°C)	−11.0 (predicted average)	U.S. EPA (2021a)
Boiling pt. (°C)	96.4 (experimental average)	
Density (g/cm^3)	1.59 (predicted average)	
pH (unitless)	NA	
pK_a (unitless)	NA	
Vapor pressure (mm Hg)	19.4 (predicted average)	
Henry's Law constant (atm-m^3/mole)	3.64e−6 (predicted average)	
Water solubility (mol/L)	0.291 (predicted average)	
Octanol-water partition constant (log K_{ow})	1.79 (predicted average)	
Bioconcentration factor (unitless)	3.57 (predicted average)	

NA = not available.

METHODS

For this assessment, the general systematic review steps common to other assessments (e.g., in Integrated Risk Information System [IRIS]) were applied, including the development of populations, exposures, comparators, and outcomes (PECO) criteria for inclusion and literature search and screening of multiple databases for relevant articles.

Briefly, methods used here are consistent with the *ORD Staff Handbook for Developing IRIS Assessments* (Version 2.0, referred to as the draft "IRIS Handbook") (U.S. EPA, 2022b). These methods were reviewed by the National Academy of Sciences (NASEM, 2021, 2018) and used in other peer-reviewed systematic reviews (Yost et al., 2019; Radke et al., 2018). The purpose of this human health assessment is to develop scientifically supported chronic toxicity values, where data are available. Less emphasis is placed on providing definitive judgments of the integrated weight of evidence.

The systematic review methods used to collect epidemiological and toxicological evidence for PFPrA are described in detail in Carlson et al. (2022) and Radke et al. (2022)[3], as well as Appendix A. PFPrA was included in the list of 150 PFAS described in those materials, and for the purposes of this summary, the PFPrA-specific results found were isolated as a result of the outlined processes. In addition to database searches, nonconfidential business information (non-CBI) industry studies were identified that included toxicological evidence for PFPrA. Since February 2020, EPA has requested, pursuant to section 308 of the Act, 33 U.S.C. § 1318, that 3M provide information on its use and possible release of certain PFAS, such as PFPrA. Under that agreement, 3M shared internal files of memos, reports, interim or final data summaries or studies, correspondence, etc. that included non-CBI content for PFPrA. The available information for PFPrA received from 3M was screened for relevance to the PECO criteria (see Figure 1). Literature identified as relevant from the database searches or non-CBI data repositories underwent data extraction and study evaluation (see documentation in Health Assessment Workspace Collaborative [HAWC]: https://hawcprd.epa.gov/assessment/100500281/).

[3] A literature search update has been conducted for PFPrA in December 2021 for the purposes of this assessment since the publication of the evidence map; therefore, the literature search and screening results presented here may differ from those described in Carlson et al. (2022) and Radke et al. (2022).

RESULTS

Literature Search and Screening Results

The database searches yielded 352 unique references for PFPrA. As shown in Figure 1, three human, one animal, and two genotoxicity studies from the 352 initial references with information relevant to understanding the potential health effects of PFPrA were identified.

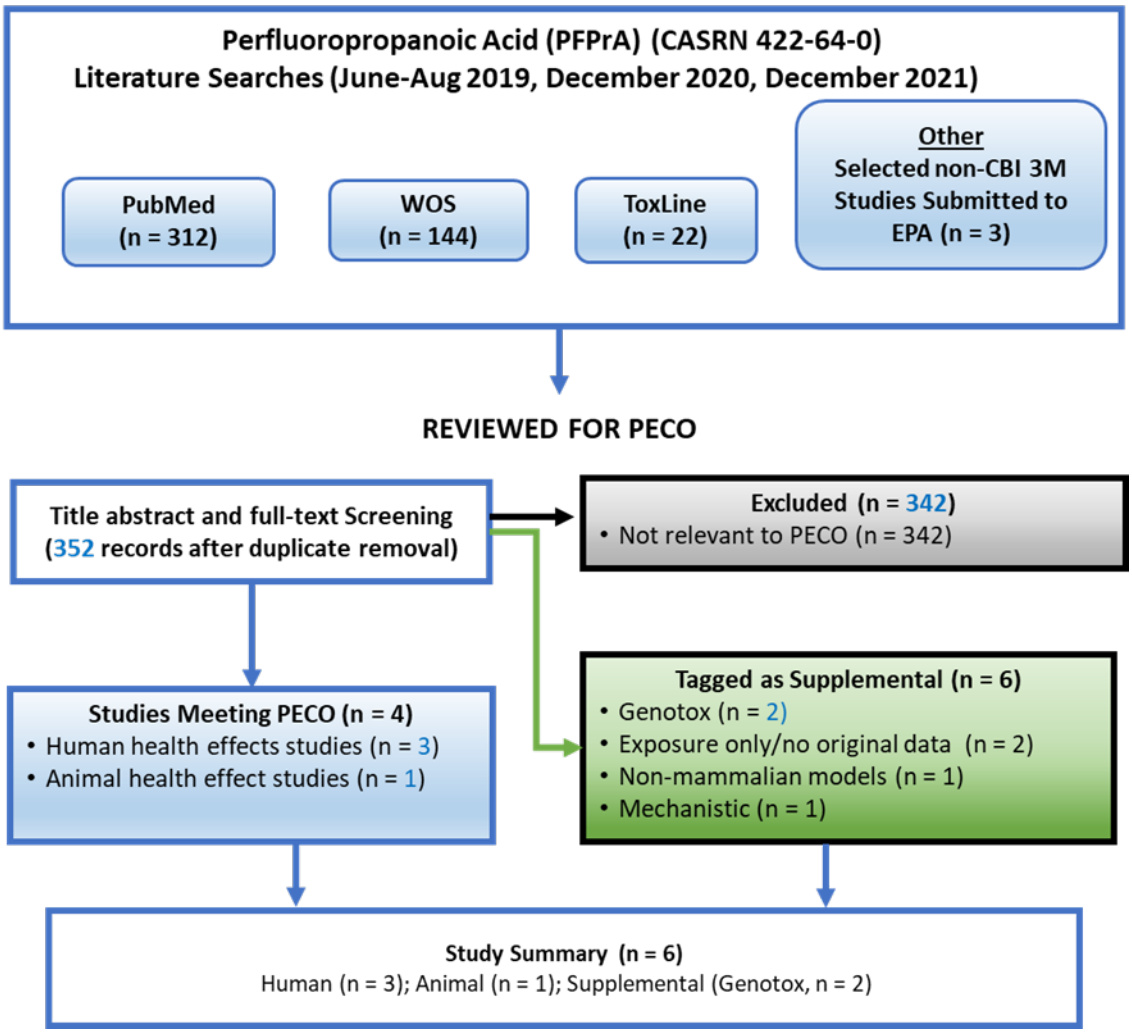


Figure 1. PFPrA Literature Search Flow Diagram

Human Studies

Three studies (Duan et al., 2020; Song et al., 2018; Li et al., 2017) examining associations of health effects with PFPrA blood concentrations in humans were identified (see Table 2). All three studies were general population cross-sectional analyses conducted in China. Adults were the primary subject in each case; a portion of the study sample in Li et al. (2017) was younger than 18 years, but the authors did not conduct sub-analyses by lifestage. One study

was rated at an overall *medium* confidence (Duan et al., 2020), and two were rated *low* confidence (Song et al., 2018; Li et al., 2017) (see Figure 2 and HAWC link for details on study confidence ratings). All three studies were rated as *deficient* for study sensitivity due to narrow concentration contrasts (Duan et al., 2020; Song et al., 2018; Li et al., 2017) or small sample size (Duan et al., 2020; Song et al., 2018; Li et al., 2017), so null findings should not be interpreted as evidence of no effect. Further details on the specific studies, concentration measurements, and chemicals evaluated are available in the interactive HAWC link.

Specific Studies

Duan et al. (2020)

One *medium* confidence cross-sectional study of nondiabetic Chinese adults examined the association between serum PFPrA concentrations and glycemic indicators (Duan et al., 2020). Participants provided an overnight fasting blood sample. Serum fasting glucose and HbA1c (a form of hemoglobin linked to sugar and a biomarker for prediabetes or type 2 diabetes) were measured. Concurrent measurement of serum PFPrA concentrations and outcome was considered adequate due to the potential for short-term responses in these outcomes. In unadjusted linear regression models, serum PFPrA was significantly associated with decreasing HbA1c levels. After adjustment for potential confounders (sex, age, body mass index, smoking and alcohol use, exercise, education, and family history of diabetes), however, the effect was no longer significant (β [95% confidence interval]: −0.012 [−0.026, 0.002]). A significant interaction (*p*-interaction = 0.024) with body mass index was observed for the association between serum PFPrA levels and HbA1c. When stratified by age (<55 and ≥55 years), the association for HbA1c was not significant for either group, although the direction of effect was similar to that of the combined analysis. The association for fasting glucose was in the same direction as for HbA1c but was not statistically significant before or after adjustment. The biological significance of decreasing HbA1c levels in association with serum PFPrA concentrations is unclear.

Li et al. (2017)

One *low* confidence cross-sectional study examined the association between PFPrA concentrations and thyroid hormones (Li et al., 2017). Adult and child participants with normal thyroid function and with thyroid disease (i.e., hyperthyroidism, hypothyroidism, and Hashimoto's disease) in China provided serum samples for analysis of PFAS and thyroid hormones. The analysis included thyroid stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), thyroglobulin antibody (TGAb), and thyroid microsomal antibody (TMAb). This study was *low* confidence due to multiple concerns for risk of bias. Details on recruitment and participation were limited, and, for those participants without thyroid disease, the reason for presentation to the hospital was not clear. Potential confounding by socioeconomic status and other factors was a concern. Additionally, timing of outcome assessment was unaccounted for in the analysis or design. Inconsistent timing of outcome assessment could lead to outcome misclassification due to the diurnal variations in thyroid hormones. Bivariate correlations of PFPrA concentrations and thyroid hormones and antibodies revealed no statistically significant associations (all correlation coefficients ranged from −0.05 to −0.1, except for FT3 in participants with hypothyroidism, r = 0.4). Only statistically significant associations were carried forward to linear regression analysis, which included adjustment for

confounding. Quantitative results for multivariable linear regression were not reported for PFPrA due to lack of statistical significance.

Song et al. (2018)

One *low* confidence cross-sectional study examined the association between PFPrA concentrations and semen parameters (Song et al., 2018). Men at an infertility clinic in China were recruited; reasons for visiting the infertility clinic were not provided, but only men without genital damage, venereal disease, or azoospermia were included in the study. The association between PFPrA concentrations and semen parameters was examined separately for PFPrA concentrations in serum and semen. This study was *low* confidence due to lack of adjustment for potential confounders and limited information on participant selection and semen collection and analysis. No statistically significant effects were identified for semen quality parameters using concentrations from either biomonitoring matrix, and the direction of association was inconsistent in serum and semen for both sperm motility and concentration.

Summary

In summary, evidence on the health effects of PFPrA in human epidemiological studies is limited. No clear associations were observed with glycemic indicators, thyroid hormones, or semen parameters. No effects of PFPrA concentrations were reliably identified in the available human studies; due to poor sensitivity across the available studies, however, this should not be interpreted as evidence of no effect.

Table 2. Associations Between PFPrA Concentrations and Health Effects in Human Epidemiological Studies

Reference, Confidence	Location, Years	Design	Population Ages (N)	Concentration Matrix and Levels (ng/mL)	Outcome	Comparison	Select Results[a]
General Population							
Duan et al. (2020) *Medium* (see HAWC link for details)	China, 2017	Cross-sectional	Adults 19–87 years old (N = 252)	Serum; Median (25th–75th percentile): 0.48 ng/mL (0.24–0.82), 23% BLOD	Fasting glucose (nmol/L), HbA1c (%)	Regression coefficient (per 1% increase serum PFPrA)	Glucose (fasting): −0.007 (−0.021, 0.008) *p*-value = 0.380 HbA1c: −0.012 (−0.026, 0.002) *p*-value = 0.099
Li et al. (2017) *Low* (see HAWC link for details)	China, 2013–2014	Cross-sectional	Children to adults 1 month–90 years old (N = 202)	Serum; 91% above LOD Median (min–max): 0.16 ng/mL (<LOD–6.1), 9% BLOD	FT3, FT4, TSH, TGAb, TMAb	Pearson correlation coefficients	Total study population: FT3: 0.027 FT4: 0.032 TSH: −0.042 TGAb: 0.001 TMAb: −0.013 Quantitative multivariable results not reported, stated as $p > 0.05$
Song et al. (2018) *Low* (see HAWC link for details)	China, 2012–2013	Cross-sectional	Men (N = 103)	Median (5th–95th percentile) Serum: 0.62 ng/mL (0.21–2.1) Semen: 0.95 ng/mL (0.29–4.1) 0% BLOD in both matrices	Semen concentration (10^6/mL), progressive motility (%)	Spearman correlation coefficients	Semen concentration, Serum: −0.112 Semen: 0.114 Progressive motility, Serum: 0.176 Semen: −0.180

BLOD = below the limit of detection; FT3 = free triiodothyronine; FT4 = free thyroxine; HbA1c = form of hemoglobin linked to sugar; LOD = limit of detection; TGAb = thyroglobulin antibody; TMAb = thyroid microsomal antibody; TSH = thyroid stimulating hormone.
[a]Results reported as effect estimate (95% confidence interval) unless otherwise specified. In some cases, presented results are constrained to those models or comparisons that most fully addressed major sources of potential bias.

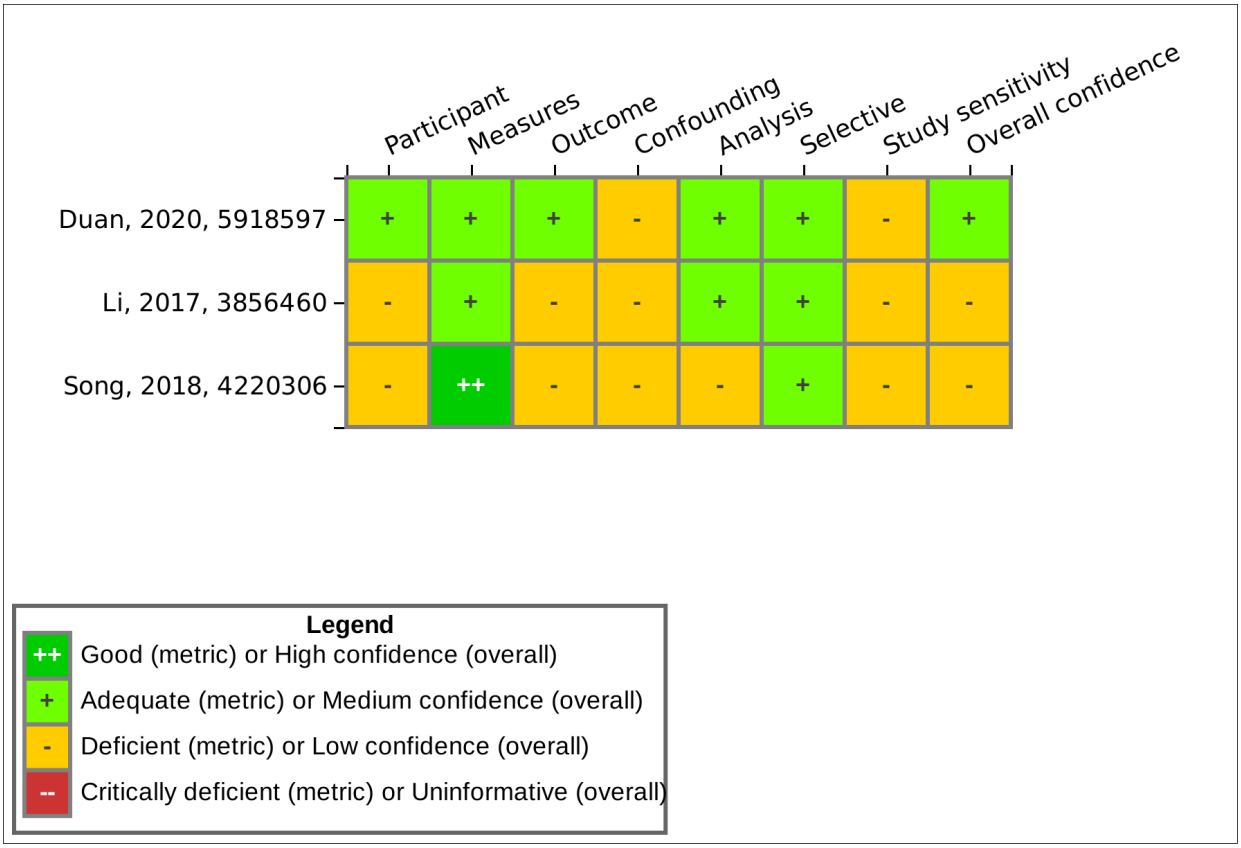


Figure 2. Summary of Study Evaluation for Human Epidemiological Studies of PFPrA and All Health Outcomes

Interactive figure and additional study details available on HAWC.

Animal Studies

A single repeat dose study is available that evaluates the toxicity of PFPrA after oral exposure (CERI, 2002c) (see Table 3). The available study is a 28-day exposure in 5-week-old male and female Crj:CD (SD) IGS rats (SPF). To determine a dose range for the 28-day study, a 14-day study was first performed that included doses of 50, 250, or 1,000 mg/kg-day. Effects on hematological parameters and organ weights were found in all dose groups after 14 days of oral exposure. Clinical chemistry abnormalities and necropsy findings were reported in the mid- and high-dose groups and clinical signs of toxicity, changes in body weights, and histopathology were reported in the high-dose group. No other details regarding the 14-day study design (e.g., number and sex of the animals) methods of endpoint evaluation, or quantitative exposure-response data were provided. The results of the 14-day study informed the authors' selection of doses for the 28-day study: Male and female rats (n = 6 per dose group and sex) were exposed via daily oral gavage to 0, 5, 20, 80, or 320 mg/kg-day PFPrA in water for 28 consecutive days. Additional control and high-dose animals were maintained for a 14-day recovery period. The study was conducted according to Organization for Economic Cooperation and Development (OECD) and Good Laboratory Practice (GLP) guidelines and evaluated clinical signs, body weights, food intake, hematology, blood chemistry, urinalysis, organ weights (liver, kidneys,

testes, ovaries, brain, spleen, adrenals) and histopathology (forestomach, glandular stomach, intestine [duodenum, jejunum, ileum, cecum, colon, rectum], liver, heart, kidneys, spleen, adrenals). Confidence is *high* in the study for all endpoints evaluated, with no significant concerns for potential bias or insensitivity (see Figure 3).

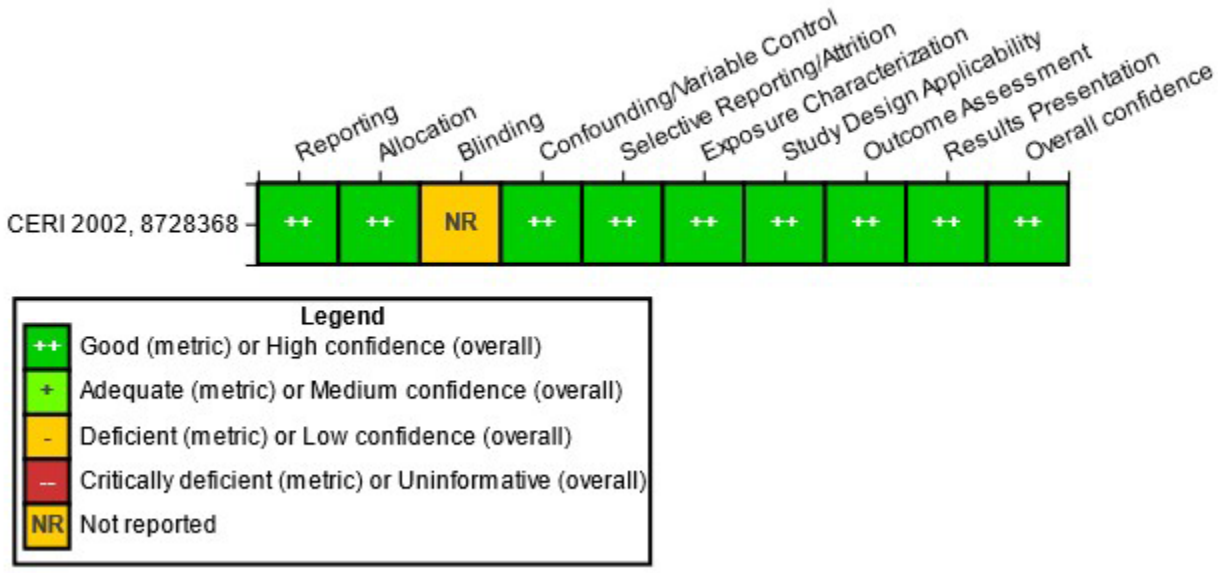


Figure 3. Summary of Study Evaluation for Experimental Animal Toxicological Studies of PFPrA and All Health Outcomes

Interactive figure and additional study details available on HAWC.

No significant effects on body weight or food intake were reported in rats with doses up to 320 mg/kg-day. Clinical signs of toxicity occurred in both males and females at the high dose and included decreased movement (8/12 males and 4/12 females) and increased salivation (9/12 males and 6/12 females). The salivation was noted to occur right after dosing and was associated with mucosal irritation and hyperplasia of squamous epithelium in the limiting ridge of the forestomach in females (4/6 animals). Loss of hair and exude/scab formation were observed in 1/6 males in the 5 and 80 mg/kg-day dose groups.

Dose-related increases in liver weights (absolute and relative) were reported in male rats (see Figure 4). Relative liver weight, the preferred metric for this organ based on its proportional relationship to body weight (Bailey et al., 2004), increased 14%–36% at ≥20 mg/kg-day in males, reaching statistical significance at 80 and 320 mg/kg-day. Marginal, non-statistically significant increases in relative liver weight were observed in the females of the same dose groups (7% and 9% at 80 and 320 mg/kg-day, respectively). Increased relative liver weights persisted after the recovery period in the 320 mg/kg-day males.

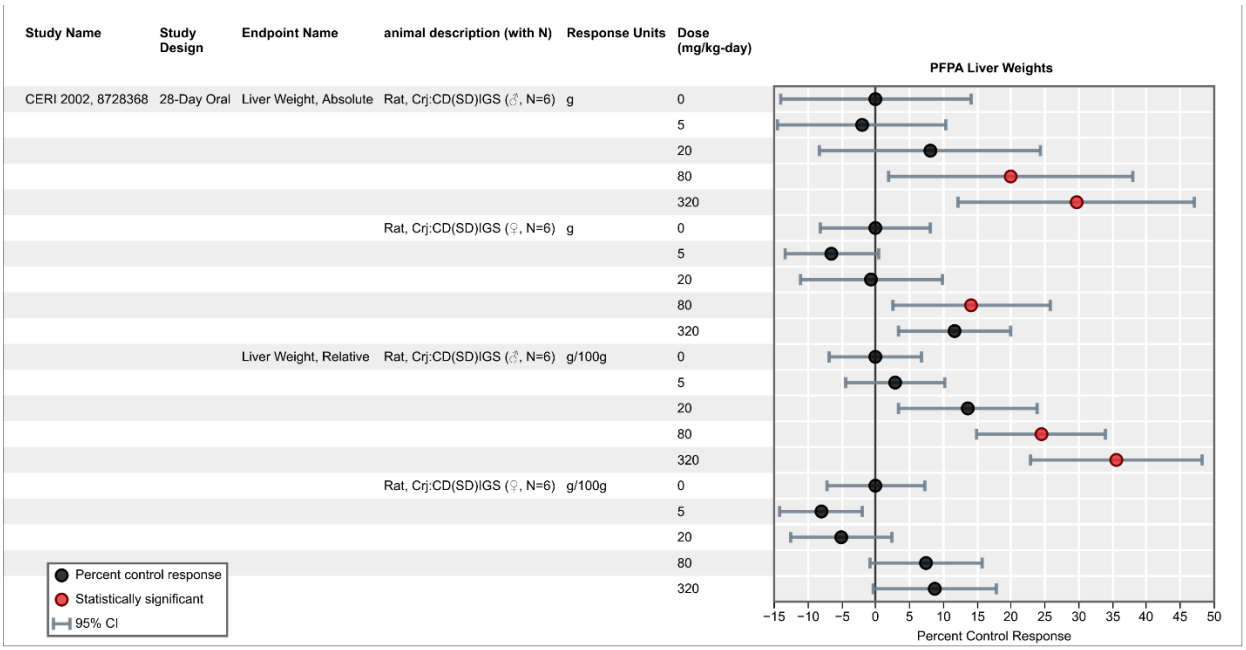


Figure 4. Liver Weight Changes in Rats Following Oral Expose to PFPrA

Interactive figure available on HAWC.

The liver weight increases in males were accompanied by noticeable enlargement of the liver at necropsy in the 320 mg/kg-day dose group and increased incidence of centrilobular hypertrophy (slight to moderate severity) at the two highest doses (2/6 and 6/6 animals at 80 and 320 mg/kg-day, respectively) (see Figure 5). Slight, focal necrosis was observed in 1/6 males in both the 20 and 80 mg/kg-day dose groups. These liver lesions were not observed in the controls or in females (0, 20, 80 and 320 mg/kg-day dose groups were evaluated in males and 0 and 320 mg/kg-day dose groups were evaluated in females for liver histopathology). Livers were no longer visibly enlarged nor were any microscopic lesions noted in males following the 14-day recovery period.

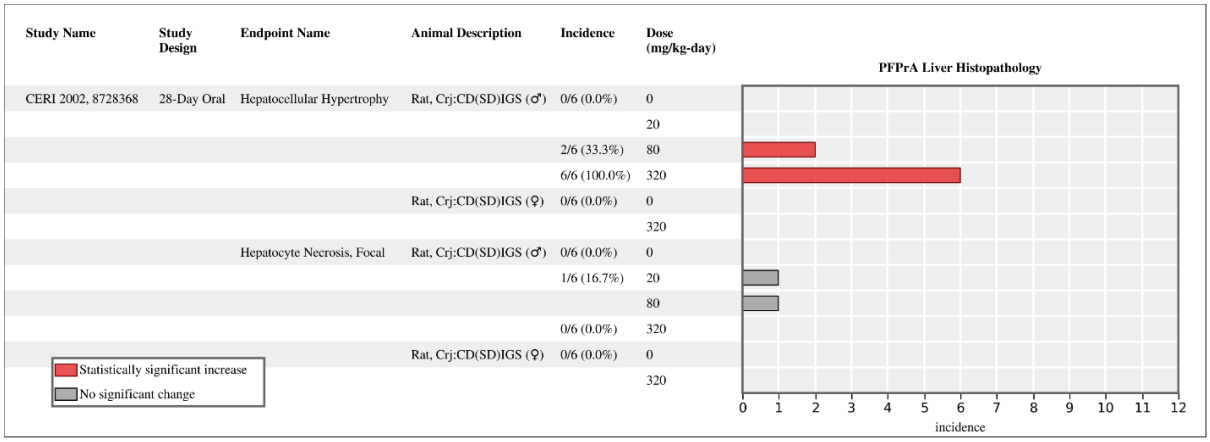


Figure 5. Liver Histopathology in Rats Following Oral Expose to PFPrA

Interactive figure available on HAWC.

Serum enzyme levels were also examined in the 28-day rat study (CERI, 2002c) (see HAWC figure for more details). Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are markers of hepatocellular damage, while alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) are markers of hepatobiliary damage (Hall et al., 2012; EMEA, 2008; Boone et al., 2005). In males, ALT and ALP levels showed an increasing trend ($p < 0.05$) across dose groups, reaching statistical significance at the highest dose (40% at 320 mg/kg-day) for ALT and at 80 mg/kg-day (30%) for ALP. Levels of AST and GGT were not significantly elevated in either male or female rats. Effects in other clinical markers relevant to liver function were also reported. Blood proteins such as albumin and globulin are routinely evaluated in clinical chemistry and changes in the levels of these blood proteins can be indicators of kidney or liver damage (Whalan, 2015). The albumin/globulin (A/G) ratio was significantly increased in all dose groups in males (15%–25%), and albumin levels were slightly elevated in the high-dose male group (4%); the increases in albumin and A/G ratio displayed a significant trend. Significant decreases in total bilirubin occurred in males (33% in all dose groups) and in females (44% at doses ≥80 mg/kg-day), but the biological significance of this decrease is unclear. Although results were not always coherent across endpoints, changes in some serum markers provide support for potential liver damage in PFPrA-exposed animals (i.e., increased ALT and ALP, and possibly A/G ratio).

Other health effects were observed in rats after 28 days of exposure, but they generally occurred only at the highest dose, were sporadic, or were not supported by corroborative evidence of toxicity. For example, kidney weight changes were observed in male and female rats but were not accompanied by significant histological lesions or biochemical indicators of kidney toxicity in the blood or urine. Indeed, female absolute kidney weights were significantly increased ($p < 0.05$) in the 80 mg/kg-day group only (16%), with a 10% increase also observed in the 20 and 320 mg/kg-day groups. Similarly, the relative kidney weights in females were significantly increased at 80 mg/kg-day (9%, $p < 0.05$). Absolute kidney weights in males were increased by 10% or more in the 80 and 320 mg/kg-day groups, but the changes were not statistically significant. Relative kidney weights were significantly increased in males exposed to ≥20 mg/kg-day (15%–18%, $p < 0.05$).

Sporadic, statistically significant changes in clinical chemistry also occurred, mainly in male rats. An increase in cholinesterase (73%) and a decrease in calcium (5%) were reported in males exposed to 80 mg/kg-day. Activated partial thromboplastin time was increased by 11%–18% in females at ≥5 mg/kg-day but did not follow a dose-response and was not accompanied by changes in platelets or prothrombin time. Total cholesterol was decreased (31%–41%) in males in all exposure groups. The biological significance of these changes in the absence of additional data is unclear.

In summary, the liver appears to be a primary target organ for PFPrA after short-term oral exposure, with male rats more sensitive than female rats. Coherent liver effects in males were reported at ≥20 mg/kg-day across organ weights, histopathology, and clinical serum markers, including dose-related increases in relative liver weights, hepatocyte lesions (mainly centrilobular hypertrophy but also some evidence of degenerative changes [slight focal necrosis]) and changes in serum markers indicative of hepatocellular/hepatobiliary injury (i.e., increased ALT and ALP).

Table 3. Available Experimental Animal Oral Toxicity Data for PFPrA

Species (Strain), Study Details	Dose (mg/kg-d)	Critical Effects	Other Effects	Reference, Confidence
Acute				
No data available.				
Short-term				
Rat (Crj:CD [SD] IGS) 28-d Oral gavage	0, 5, 20, 80, 320	Increased relative liver weight in males at ≥20 mg/kg-d, accompanied by hepatocyte lesions (primarily hypertrophy with some evidence of slight focal necrosis) and serum markers of hepatocellular/hepatobiliary injury (i.e., increased ALT, ALP) at ≥80 mg/kg-d	Decreased movement and increased salivation after treatment; increased activated partial thromboplastin time, albumin, albumin/globulin ratio, kidney weight; decreased total cholesterol, total bilirubin; increased incidence of forestomach lesions	CERI (2002c) *High*
Subchronic				
No data available.				
Chronic/Carcinogenicity				
No data available.				
Reproductive/Developmental				
No data available.				

ALT = alanine aminotransferase; ALP = alkaline phosphatase.

Other Data

Other human health relevant studies conducted on PFPrA include an Ames test to evaluate genotoxicity and a chromosomal aberration study (see Table 4). For the Ames test, a dose range finding study and a main study were conducted (CERI, 2002a). The main study included five concentrations ranging from 313 to 5,000 µg/plate with the highest dose of 5,000 µg/plate diluted for the remaining four doses with a geometric progression of two. The compound was found not to have potential for mutagenicity. In the chromosomal aberration test, Chinese hamster lung fibroblasts were exposed to concentrations of 0, 410, 820, or 1,640 µg/mL of PFPrA, and no increase was found in the frequencies of cells with total aberrations (chromatid breaks, chromatid exchanges, chromosome breaks, chromosome exchanges) using the short-term or the continuous treatment methods (CERI, 2002b). Growth inhibition tests, including concentrations as low as 6.41 µg/mL, demonstrated some inhibition at the 1,640 µg/mL concentration using the short-term method and at concentrations ≥205 µg/mL in the continuous treatment method, but no increases in structural or numerical aberrations.

Table 4. Summary of PFPrA Genotoxicity Studies

Endpoint	Test System	Concentrations Tested	Results Without Activation[a, b]	Results With External Activation[a, b]	References
Ames Assay (revertant colonies)	*Salmonella typhimurium* (TA100, 1535, 98, 1537), *Escherichia coli* (WP2 *uvrA*) in the presence and absence of metabolic activation system (S9 mix)	0, 313, 625, 1,250, 2,500, 5,000 µg/plate	–	–	CERI (2002a)
Chromosomal aberration	Chinese hamster lung fibroblasts with or without S9 mix	0, 410, 820, 1,640 µg/mL	–	–	CERI (2002b)

[a]Results reported as – = negative.

DERIVATION OF REFERENCE VALUES

The hazard and dose-response database for PFPrA is limited to studies via the oral route of exposure. There are no known inhalation or dermal studies for PFPrA. Further, no known studies have evaluated potential cancer effects of PFPrA, and studies relevant to potential cancer mechanism(s) are sparse and inconclusive. The purpose of this assessment is to inform human health hazard(s) associated with chronic duration/lifetime exposures to PFPrA. Therefore, only a noncancer chronic reference dose (RfD) is derived in this assessment for the oral route of exposure. The RfD derived in this assessment is an estimate of an oral exposure to the human population (including susceptible subgroups and lifestages) likely to be without an appreciable risk of adverse health effects over a lifetime.

Derivation of Oral Reference Dose

The hazard and dose-response database for PFPrA is limited to one *medium* confidence (Duan et al., 2020) and two *low* confidence (Song et al., 2018; Li et al., 2017) epidemiological studies that evaluated potential associations between health effects and PFPrA blood serum concentrations in humans, and one *high* confidence repeat-dose (28-day) oral gavage study in rats [conducted by the Chemicals Evaluation and Research Institute, Japan; (CERI, 2002c)]. Two of the three human studies have multiple limitations discussed previously (see the Human Studies summaries for more details) that diminish confidence in reported associations and decrease their ability to inform conclusions. In addition, studies that used measurements of biomarkers in tissues or bodily fluids as the metric for exposure were considered suitable only for dose-response analysis if data or physiologically based pharmacokinetic (PBPK) models are available to extrapolate between the reported biomarker measurement and the route-specific level of exposure. As such, the human studies were not considered further for toxicity value derivation.

The 28-day oral rat study CERI (2002c) was conducted consistent with OECD guideline protocol and under GLP conditions and had an overall *high* confidence rating based on a study quality evaluation (see HAWC link for more details). Male and female control and PFPrA-treated rats were evaluated across a comprehensive panel of general toxicity, clinical chemistry, organ weight, and histopathological parameters. The liver of rats was identified as a primary target of PFPrA toxicity following 28 days of oral exposure; male rats were more sensitive than females across all parameters evaluated and thus were prioritized for dose-response analyses. Alterations included increases in relative liver weights at ≥20 mg/kg-day and increased absolute liver weights in males at ≥80 mg/kg-day; gross enlargement of the liver and histopathological indicators of altered tissue architecture or injury (e.g., centrilobular hypertrophy; some evidence of focal necrosis) at ≥80 mg/kg-day; and increased serum enzymes indicative of hepatic injury (i.e., ALT and ALP) at ≥80 mg/kg-day. According to Hall et al. (2012), this constellation of effects is consistent with criteria supporting a determination of liver injury. Specifically, the PFPrA-induced liver effects are indicative of an interrelated pattern of toxicity to parenchymal (i.e., hepatocyte hypertrophy, necrosis, and ALT release into systemic circulation) and nonparenchymal (e.g., hepatic biliary epithelial release of ALP into systemic circulation) cell populations. Despite the lack of additional oral repeat-dose studies examining liver effects of PFPrA by which to evaluate similarity of results, this profile of PFPrA-induced liver effects is consistent with liver toxicity observed in experimental rodents following oral exposure to perfluorobutanoic acid, a closely related linear short-chain (4-carbon) perfluorocarboxylic acid

(U.S. EPA, 2021e). These effects observed in animals are considered relevant for humans in the absence of experimental data that provide direct information to the contrary. In total, evidence in animals indicates that PFPrA exposure may cause liver effects in humans, but few studies were available to contribute to the evaluation. The main study that this conclusion is based on assessed dose levels of 5–320 mg/kg-day and was conducted according to well-established experimental animal guidelines (CERI, 2002c). Despite limitations in the availability of repeat-dose toxicity studies in the database (including in species other than rat), the 28-day rat study by CERI (2002c) was considered for the derivation of a chronic RfD for PFPrA. The RfD for PFPrA may be useful for certain decision contexts, such as providing a sense of the magnitude of potential human health risks, ranking potential hazards, or informing PFAS mixtures assessment in which PFPrA is a component (U.S. EPA, 2005, 2000).

The PFPrA-induced liver effects observed in male rats from the CERI (2002c) 28-day study were evaluated for amenability to benchmark dose (BMD) modeling (see Table 5). Consistent with EPA's *Benchmark Dose Technical Guidance* (U.S. EPA, 2020a, 2012, 2002), the BMDs and 95% lower confidence limits on the BMDs (BMDLs) for increased relative liver weight, serum ALT, serum ALP, and incidence of hepatocyte hypertrophy were estimated using a benchmark response (BMR) representative of a biologically or statistically significant level of change for continuous (e.g., relative liver weight; serum ALT and ALP) or dichotomous (e.g., incidence of hepatocyte hypertrophy) endpoints. For liver weight changes, a 10% increase over control is considered biologically significant for this assessment. For serum ALT and ALP, a 1-standard deviation (SD) change over control was used. For hepatocyte hypertrophy, a 10% increased incidence over control was used (U.S. EPA, 2020a, 2012, 2002). The full results of the BMD modeling are provided in Appendix B.

Table 5. Data for Liver Effects in Adult Male Crj:CD (SD) IGS (SPF) Rats Exposed to PFPrA for 28 Days via Gavage (CERI, 2002c)

Endpoint	Dose, mg/kg-d[b]				
	0	**5**	**20**	**80**	**320**
Relative liver weight – % of BW[a]	3.15 ± 0.19	3.24 ± 0.21 (+3%)	3.58 ± 0.34* (+14%)	3.92 ± 0.29** (+24%)	4.27 ± 0.43** (+36%)
Serum ALT – IU/L[a]	25 ± 5	27 ± 3 (+8%)	27 ± 2 (+8%)	29 ± 4** (+16%)	35 ± 4 (40%)
Serum ALP – IU/L[a]	420 ± 48	428 ± 74 (+2%)	242 ± 83 (+1%)	545 ± 79** (+30%)	518 ± 107 (23%)
Hepatocyte hypertrophy – incidence	0	ND	0	2	6
Animals (*n*)	6	6	6	6	6

ALT = alanine aminotransferase; ALP = alkaline phosphatase; BW = body weight; ND = not determined.
[a]Values expressed as mean ± SD. Parentheses show % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
[b]Dosimetry: Oral rat exposures are expressed in mg/kg-day as reported by the study authors.
*Biologically significant change from control. **Statistically ($p \leq 0.05$) and biologically significant change from control.

Following dose-response modeling of the liver effect data in male rats, BMDLs were converted to corresponding human equivalent doses (HEDs) (see Table 6). In *Recommended Use*

of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose (U.S. EPA, 2011), EPA endorses a hierarchy of approaches to derive human equivalent oral exposures from data on laboratory animal species, with the preferred approach being physiologically based toxicokinetic modeling. Without a complete physiologically based toxicokinetic model, other approaches might include using available chemical-specific information (e.g., clearance or plasma half-life values). In the absence of chemical-specific models or data to inform the derivation of human equivalent oral exposures, EPA recommends doses be scaled allometrically using body weight (BW)$^{3/4}$ as a default method to extrapolate toxicologically equivalent doses of orally administered agents from laboratory animals to humans to derive an RfD, under certain exposure conditions. For PFPrA, no toxicokinetic data were identified, so no chemical-specific data are available to inform cross-species kinetics between rats and humans[4]. As such, the male rat BMDLs were converted to the human equivalent points of departure (POD_{HEDs}) using default $BW^{3/4}$ scaling. Table 6 provides the candidate points of departure (i.e., POD_{HEDs}) obtained from the BMD-modeled liver effects data from male rats of the 28-day study (CERI, 2002c).

Table 6. Candidate PODs for Derivation of the Chronic RfD for PFPrA

Endpoint	BMDL mg/kg-d	POD type	POD_{HED}[a] mg/kg-d	Reference
Increased relative liver weight in adult males	6.3	$BMDL_{10}$	1.6	CERI (2002c)
Increased hepatocyte hypertrophy in adult males	7.9	$BMDL_{10}$	2.0	CERI (2002c)
Increased serum ALP in adult males	20	$BMDL_{1SD}$	5.0	CERI (2002c)
Increased serum ALT in adult males	28	$BMDL_{1SD}$	7.0	CERI (2002c)

ALP = alkaline phosphatase; ALT = alanine aminotransferase; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 10 = dose associated with a 10% extra risk in parameter, 1SD = dose associated with 1 standard deviation relative risk from the control); BMR = benchmark response; POD = point of departure; POD_{HED} = human equivalent point of departure.

[a]HEDs were calculated using species-specific application of a dosimetric adjustment factor (DAF), as recommended by U.S. EPA (2011). The DAFs are calculated as follows: $DAF = (BW_a^{1/4} \div BW_h^{1/4})$, where BW_a = animal body weight, and BW_h = human body weight. Default body weight for male SD-derived rats (0.267 kg [for subchronic duration]) and a reference body weight of 80 kg for humans, as recommended in U.S. EPA (1988), were used to calculate the DAFs.

Considering that confidence among the candidate points of departure (PODs) is approximately equivalent (i.e., the same study population/species, exposure paradigm, and quality of exposure and outcome measurement), the POD_{HED} of 1.6 mg/kg-day for increased relative liver weight represented the most sensitive effect in rats and was identified as the POD

[4] To inform cross-species extrapolation for PFPrA, toxicokinetic (TK) data for PFBA, a closely related linear short-chain (4-carbon) perfluorocarboxylic acid, was considered. For PFBA, TK data exist in relevant animals and humans, leading to a data-informed extrapolation approach (i.e., ratio of the clearance (CL) in humans to animals, CL_H:CL_A) for estimating the DAF in U.S. EPA (2021e). For comparison, the DAF for PFPrA, based on the default $(BW)^{3/4}$ approach in male rats, is 0.25 which is similar to the data-informed DAF for male rats for PFBA of 0.229.

for deriving a chronic RfD for oral PFPrA exposure. Under EPA's *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002) and *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994), five possible areas of uncertainty and variability were considered in deriving the chronic RfD for PFPrA. The chronic RfD is derived by applying a composite uncertainty factor (UF_C) of 3,000 (reflecting an interspecies uncertainty factor [UF_A] of 3, an intraspecies uncertainty factor [UF_H] of 10, a duration uncertainty factor [UF_S] of 10, and a database uncertainty factor [UF_D] of 10) to the POD_{HED} of 1.6 mg/kg-day. Table 7 summarizes the uncertainty factors for the chronic RfD for PFPrA. Confidence in the chronic RfD for PFPrA is *low*, as described in Table 8. The *low* confidence in the chronic RfD, resulting primarily from the limited available hazard and dose-response relevant evidence in the database, indicate a high level of uncertainty in the derived RfD. Nevertheless, this RfD may be useful for some decision purposes (U.S. EPA, 2005).

Chronic RfD = $POD_{HED} \div UF_C$
= 1.6 mg/kg-day ÷ 3,000
= **0.0005 or 5×10^{-4} mg/kg-day**

Table 7. Uncertainty Factors for the Chronic RfD for PFPrA (CASRN 422-64-0)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty in characterizing the toxicokinetic and toxicodynamic differences between animals and humans following oral PFPrA exposure. Cross-species dosimetric adjustment (HED calculation) was performed using default allometric $BW^{3/4}$ scaling between rats and humans. This scaling is applied to account for some aspects of the cross-species toxicokinetic processes. Further, cross-species toxicokinetic (TK) data for PFBA, a closely related linear short-chain (4-carbon) perfluorocarboxylic acid, was considered. For PFBA, TK data exist in relevant animals and humans, leading to a data-informed extrapolation approach (i.e., ratio of the clearance (CL) in humans to animals, CL_H:CL_A) for estimating the DAF as suggested in U.S. EPA (2022a). For comparison purposes, for PFPrA, the DAF of 0.25 for male rats based on the application of the default $(BW)^{3/4}$ approach is similar to the data-informed DAF for male rats for PFBA of 0.229. This suggests that although a default allometric BW scaling approach is used for the 3-carbon structure PFPrA, the resulting DAF is similar to a data-informed DAF for the 4-carbon PFBA. As such, a factor of 3 is applied to account for residual toxicokinetic uncertainty and potential toxicodynamic differences across species.
UF_D	10	A UF_D of 10 is applied to account for deficiencies and uncertainties in the database. The database for oral exposure to PFPrA is limited to three human epidemiological studies (one *medium* confidence and two *low* confidence) and a single *high* confidence, 28-day repeat-dose oral rat study. No longer-duration repeat-dose studies, examining potential systemic, reproductive, developmental or immunotoxicity effects are available following exposure via any route.
UF_H	10	A UF_H of 10 is applied to account for interindividual variability in the susceptibility of the human population because of both intrinsic and extrinsic factors that can influence the response to dose, in the absence of chemical-specific information to assess toxicokinetic and toxicodynamic variability of PFPrA in humans.
UF_L	1	A UF_L of 1 is applied because the POD is a BMDL.
UF_S	10	A UF_S of 10 is applied to account for uncertainty in how a significantly longer exposure duration might impact the incidence and or severity of liver injury. The POD was derived from a 28-day rat study; studies of PFPrA exposures for longer than 28 days were not available to evaluate and characterize the potential for increasing magnitude or incidence of injury in the liver with increasing exposure duration.
UF_C	3,000	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

BMDL = benchmark dose lower confidence limit; BW = body weight; HED = human equivalent dose; POD = point of departure; RfD = reference dose; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = less-than-chronic duration uncertainty factor.

Table 8. Confidence Descriptors for the Chronic RfD for PFPrA (CASRN 422-64-0)

Confidence Categories	Designation	Discussion
Confidence in study	H	Confidence in the principal study CERI (2002c) is *high*. The study was performed by an industry/contract lab using an established OECD protocol for 28-day oral exposures in rodents and under GLP conditions. All but one of the toxicity study rating criteria were of "Good" or "High" confidence (see Figure 3 and information available on HAWC).
Confidence in database	L	Confidence in the database for PFPrA is *low*. The relevant human health assessment database consists of one *medium* and two *low* confidence human epidemiological studies, and a single 28-day repeat-dose oral rat study. No longer-duration repeat-dose studies, examining potential systemic, reproductive, developmental or immunotoxicity effects are available following exposure via any route.
Confidence in quantification of the POD_{HED}	M	Confidence in the quantification of the POD and RfD is *medium*. The POD was based on BMD modeling within the range of the observed data. Dosimetric adjustment of the POD was based on default $BW^{3/4}$ scaling due to the lack of chemical specific toxicokinetic data (e.g., clearance, half-life).
Confidence in the chronic RfD	L	The overall confidence in the chronic RfD is *low* and is primarily driven by *low* confidence in the available database for PFPrA.

BMD = benchmark dose; BW = body weight; GLP = Good Laboratory Practice; HED = human equivalent dose; POD = point of departure; RfD = reference dose.

Derivation of Inhalation Reference Concentrations

No studies have been identified that examine noncancer effects of PFPrA via the inhalation exposure route.

Summary of Noncancer Reference Values

Noncancer reference values are summarized in Table 9.

Table 9. Summary of the Noncancer Reference Values for PFPrA (CASRN 422-64-0)

Toxicity Type (units)	Species/Sex	Critical Effect	Reference Value mg/kg-d	POD Method	POD_{HED} mg/kg-d	UF_C	Principal Study
Chronic RfD (mg/kg-d)	Rat/M	Increased relative liver weight	0.0005	$BMDL_{10}$	1.6	3,000	CERI (2002c)
Chronic RfC (mg/m^3)	NDr						

BMDL = benchmark dose lower confidence limit (subscripts denote benchmark response: i.e., 10 = dose associated with a 10% extra risk in parameter); M = male(s); NDr = not derived; POD_{HED} = human equivalent point of departure; RfC = reference concentration; RfD = reference dose; UF_C = composite uncertainty factor.

CARCINOGENICITY ASSESSMENT

No studies have been identified that examine potential carcinogenicity of PFPrA via any route of exposure.

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APPENDIX A. SYSTEMATIC LITERATURE SEARCH METHODS AND RESULTS

Methods

The following describes the systematic review methods used to collect epidemiological and toxicological evidence for ~150 PFAS as part of the larger PFAS systematic review effort described in Carlson et al. (2022); Radke et al. (2022) [3]. The methods outlined below are taken from (Carlson et al., 2022) and further details can be found directly in the published manuscript. Perfluoropropanoic acid (PFPrA) was part of the list of 150 PFAS, and for the purposes of this summary, we isolated the PFPrA-specific results found as a result of the processes outlined below.

Populations, Exposures, Comparators, and Outcomes (PECO) Criteria and Supplemental Material Tagging

PECO criteria are used to focus the scope of an evidence map or systematic review by defining the research question(s), search terms, and inclusion/exclusion criteria. The PECO criteria for PFPrA are presented in Table A-1. In addition to PECO-relevant studies, studies that did not meet PECO criteria but contained "potentially relevant" supplemental material were tracked during the literature screening process. Supplemental material was tagged by category, as outlined in Table A-2. Note that "supplemental" material does not refer to findings contained in the supplement of papers identified.

Literature Search and Screening Strategies

Database Search Term Development

Chemical search terms were used to search for relevant literature in the databases listed below. The detailed search strategy for each database, including specific search stings are presented in the supplemental materials of Carlson et al. (2022).

- PubMed (National Library of Medicine)
- Web of Science (Thomson Reuters)
- ToxLine via TOXNET (included in the 2019 search; no longer operational in the 2020 or 2021 search updates)[5]

The literature search for the ~150 PFAS consisted only of the chemical name, synonyms, and trade names and no additional limits, with the exception of the Web of Science (WoS) search strategy. Due to the specifics of searching WoS, a chemical name-based search can retrieve a very large number of off-topic references. Given the number of PFAS included in the 150 PFAS screening effort, a more targeted WoS search strategy was used to identify the records most likely applicable to human health (see supplemental materials of Carlson et al. (2022)). Chemical synonyms for PFAS were identified by using synonyms in the Dashboard (U.S. EPA, 2021a) indicated as "valid" or "good." The preferred chemical name (as presented in the Dashboard), CASRN, and synonyms were then shared with EPA information specialists who used these

[5]As part of a broader National Library of Medicine (NLM) reorganization, TOXNET has moved and most of NLM's toxicology information services have been integrated into other NLM products and services.

inputs to develop search strategies tailored for PubMed, Web of Science, and ToxLine (see supplemental materials of Carlson et al. (2022)).

Database Searches

The database searches were conducted by an EPA information specialist in August 2019 for the 150 PFAS, and searches were updated in December 2020 and again in December 2021. All records were stored in EPA's Health and Environmental Research Online (HERO) database (U.S. EPA, 2019a, b). The HERO database (https://heronet.epa.gov/heronet/index.cfm/content/home) (U.S. EPA) is used to provide access to the references used in the EPA's scientific assessments, including this effort. After deduplication in HERO using unique identifiers (e.g., PMID, WoSID, or DOI) and citations, the references went through an additional round of deduplication using ICF's Deduper tool (described in detail in the supplemental materials of Carlson et al. (2022), "DeDuper"), which uses a two-phase approach to identify duplicates by a) locating duplicates using automated logic and b) employing machine learning built from Python's Dedupe package to predict likely duplicates which are then verified manually (Magnuson et al., 2018). Following deduplication, SWIFT-Review software (Sciome, 2021; Howard et al., 2016) was used to identify which of the unique references were most relevant for human health risk assessment. In brief, SWIFT-Review was used to filter the unique references based on the software's preset literature search strategies (titled "evidence stream"). These evidence streams were developed by information specialists and can be used to separate the references most relevant to human health from those that are not (e.g., environmental fate studies). References are tagged to a specific evidence stream if the search terms from that evidence stream appear in the title, abstract, keyword, and/or medical subject headings (MeSH) fields of that reference. For the PFAS 150 SEM, the following SWIFT-Review evidence stream were applied: human, animal models for human health, and *in vitro* studies. Specific details on the evidence stream search strategies are available through Sciome's SWIFT-Review documentation at https://www.sciome.com/wp-content/uploads/2019/08/SWIFT-Review-Search-Strategies-Evidence-Stream.docx. Studies not retrieved using the search strategies were not considered further.

Other Resources Consulted

The literature search strategies described above are intentionally broad; however, it is still possible that some studies were not captured (e.g., cases where the specific chemical is not mentioned in title, abstract, or keyword content; "gray" literature that is not indexed in the databases listed above). Additionally, if incomplete citation information was provided (e.g., if reference lists searched did not include titles) no additional searching was conducted. Thus, in addition to the databases identified above, the sources below were used to identify studies that could have been missed during the database searches. Additional descriptions of these sources can be found in Table 4 of Carlson et al. (2022).

- Reference list from the PFAS-Tox Database, a 2019 evidence map of 29 PFAS (Pelch et al., 2019), available at https://public.tableau.com/profile/the.endocrine.disruption.exchange#!/vizhome/PFASToxDatabase/PFASDatabase-BETA and https://pfastoxdatabase.org/. (PFASToxDatabase)

- Reference lists from all PECO-relevant animal and epidemiological studies identified in the database searches meeting PECO criteria (see supplemental materials of Carlson et al. (2022))

- National Toxicology Program (NTP) database of study results and research projects. The was accomplished by personal communication with NTP rather than manual search of the NTP database for all the PFAS included in the evidence map.

- References from EPA's CompTox Chemicals Dashboard ToxValDB (Toxicity Values Database) (U.S. EPA, 2018) to identify studies or assessments that present POD information. ToxValDB collates publicly available toxicity dose-effect related summary values typically used in risk assessments. Many of the PODs presented in ToxValDB are based on gray literature studies or assessments not available in databases such as PubMed and WoS, etc. It is important to note that ToxValDB entries have not undergone quality control to ensure accuracy or completeness and may not include recent studies.

    - ToxValDB includes POD data collected from data sources within ACToR (Aggregated Computational Toxicology Resource) and ToxRefDB (Toxicity Reference Database) and no-observed and lowest-observed (adverse) effect level (NOEL, NOAEL, LOEL, LOAEL) data extracted from repeated dose toxicity studies submitted under REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals). Also included are reference dose and concentration values (RfDs and RfCs) from EPA's Integrated Risk Information System (IRIS) and dose descriptors from EPA's Provisional Peer-Reviewed Toxicity Values (PPRTV) documents. Acute toxicity information in ToxValDB comes from several sources, including Organization for Economic Cooperation and Development (OECD) eChemPortal, National Library of Medicine (NLM), Hazardous Substances Data Bank (HDSB), ChemIDplus via EPA Toxicity Estimation Software Tool (TEST), and the European Union (EU) Joint Research Centre (JRC) AcutoxBase and the EU COSMOS project and the European Chemicals Agency (ECHA) registration dossiers to identify data submitted by registrants, available at http://echa.europa.eu/information-on-chemicals/information-from-existing-substances-regulation. (ECHA, 2020)

Records from these other sources were uploaded into DistillerSR (Evidence Partners, 2022) and annotated with respect to source of the record. The specific methods and results for searching each source are described below. Results of searches of these sources is summarized to include the source type or name, the search string (when applicable), the number of results present within the resource, and the URL (when available and applicable).

ECHA

A search of the ECHA registered substances database was conducted using the CASRN. The registration dossier associated with the CASRN was retrieved by navigating to and clicking

the eye-shaped view icon displayed in the chemical summary panel. The General Information tab and all subpages under the Toxicological Information tab were downloaded in PDF format, including all nested reports that had unique URLs. In addition, the data were extracted from each dossier page and used to populate an Excel tracking sheet with this data. Extracted fields included data from the general information page regarding the registration type and publication dates, and on a typical ECHA dossier page the primary fields reported in the administrative data, data source, and effect levels sections. Each study summary resulted in more than one row in the tracking sheet if more than one data source or effect level was reported.

At this stage, each reference was reviewed for inclusion based on PECO criteria. ECHA dossiers without information under the ToxCategory column were excluded from review because these refer to data extracted from the General Information tab. Toxicological and end point summary pages, study protocols, and dossiers with data waiving were also excluded from review. When a reference that was considered relevant reported data from a named study or lab report, a citation for the full study was either retrieved or generated in HERO and verified that it was not already identified from the peer-reviewed literature search prior to moving forward to screening in DistillerSR. If citation information was not available and a full text could not be retrieved, ECHA and ToxValDB references were compared using information on the chemical, points of departure, study type, species, strain, sex, exposure route and method, and critical effect to determine whether any of these references were previously accounted for in ToxValDB. When there were no overlaps between references, a citation was created in HERO using the information provided in the ECHA dossier. The generated PDF for the dossier was used as the full text for screening, and these citations were annotated accordingly for Tableau and HAWC visualizations by adding "(ECHA)" to the citation.

EPA CompTox chemical dashboard (ToxValDB)

ToxValDB data was retrieved for the PFAS chemicals from the EPA CompTox Dashboard (U.S. EPA, 2018). Data available from the Hazard tab for each chemical was exported from the Dashboard by U.S. EPA staff and provided as an Excel file output. Using this ToxValDB POD summary file, citations were identified for references that apply to human health PODs. A citation for each reference, except those indicated as "ECHA" or "ECHA IUCLID," was either retrieved or generated in HERO and verified that it was not already identified from the database search prior to moving forward to screening in DistillerSR.

References in ToxValDB described as from an ECHA or ECHA IUCLID source were confirmed to be accounted for in the ECHA results retrieved above. A comparison was performed between 25% of the ECHA references from ToxValDB and the full ECHA results retrieved above, and although the comparison noted discrepancies (5 out of 34), these were found to be inaccuracies in ToxValDB, most likely because the data was removed or modified during an update to ECHA since the last time ToxValDB imported ECHA data. That is, the ECHA dossiers retrieved above were determined to be more accurate and up to date than the ToxValDB ECHA entries and could supersede the ECHA data from ToxValDB.

Screening and Tagging Process

After selection of evidence steams and chemicals in SWIFT-Review as described in the "Database Searches" section, the filtered studies were imported into SWIFT-Active Screener (version 1.061; Sciome LLC) for title or abstract (TIAB) screening. SWIFT-Active Screener is a

web-based collaborative software application that uses active machine-learning approaches to reduce the screening effort (Howard et al., 2020). The screening process was designed to prioritize records that appeared to meet PECO criteria or that included supplemental material content based on TIAB content (i.e., both types of records were screened as "include" for active-learning purposes). Studies were screened in SWIFT-Active Screener until the software indicated a likelihood of 95% that all relevant studies had been captured. This threshold is comparable to human error rates (Bannach-Brown et al., 2018; Howard et al., 2016; Cohen et al., 2006) and is used as a metric to evaluate machine-learning performance. Any studies in "partially screened" status at the time of reaching the 95% threshold were fully screened.

Studies that met these criteria from TIAB screening were then imported into DistillerSR (Evidence Partners, 2022) for more specific TIAB tagging (i.e., to separate studies meeting PECO criteria versus supplemental content and to tag the specific type of supplemental content and, if necessary, the chemical). Supplemental content tags are described in Table A-2. For studies meeting PECO criteria at the DistillerSR TIAB level, full text articles were retrieved through EPA's HERO database. References that could be retrieved within 45 days were identified to be unavailable.

Studies identified via the gray literature searches were imported directly into DistillerSR at the TIAB phase. References identified in the gray searches that had previously been screened as not relevant to PECO criteria at either the SWIFT-Review or SWIFT-Active Screener stage were rescreened in Distiller.

Two independent reviewers conducted each level of screening (TIAB and full text). At all levels (SWIFT-Active Screener TIAB, DistillerSR TIAB, and DistillerSR full-text review), any conflicts in screening were resolved by discussion between the two independent reviewers; a third reviewer was consulted if any conflicts remained thereafter. Conflicts between screeners in applying the supplemental tags were resolved by discussion at both the TIAB and full-text levels, erring on the side of over tagging at the TIAB level. At the TIAB level, articles without an abstract were screened based on title (title should indicate clear relevance), and number of pages (articles two pages or fewer in length were assumed to be records with no original data) For additional information, please see Table A-2 for supplemental categorization information. All studies identified as supplemental material at TIAB and full-text levels were tagged to their respective chemical(s) using the preferred chemical names. All studies identified as PECO were tagged to the preferred chemical name after the full-text screening stage. A caveat to tagging at the TIAB level was that tagging was based only on information provided in the abstract and could therefore miss additional details that may have been provided in the full text of the manuscript. Additionally, sources that did not list a specific PFAS in the TIAB (i.e., included terms like "PFAS") were tagged to "chemical not specified." However, if any PFAS were specified, they were tagged and the "chemical not specified" tag was not selected, even though it was possible that additional PFAS chemicals were reported in the full text. All chemical tagging was reviewed by an expert in chemistry (with a doctoral or similar degree). Where chemical identity presented in the manuscript was unclear, the original authors were contacted to resolve the chemical species.

Data Extraction of Study Methods and Findings

Animal Toxicology Studies

Studies that met PECO criteria after full-text review were summarized using custom forms (a standard operating procedure for populating the forms is included in the supplemental material of Carlson et al. (2022)) in DistillerSR. For animal studies, the following study summary information was captured in a literature inventory: PFAS assessed, study type [acute (<24 hours), short term (1–30 days), subchronic (30–90 days), chronic (>90 days), developmental, peripubertal, multigenerational], route of exposure, species, sex, and health system(s) assessed. For epidemiological studies, the following study summary information was captured in a literature inventory: PFAS assessed, sex, population, study design, exposure measurement (e.g., blood, feces), and health system(s) assessed. Summaries were then extracted into DistillerSR by one team member, and the extracted data were checked for quality by at least one other team member. The data from these summary literature inventories were exported from DistillerSR to an Excel format and then modified and transformed using Excel's 'Get and Transform' features for import into Tableau visualization software (https://www.tableau.com/) (version 2019.4; Tableau Software LLC) (Tableau Software, 2023). These data transformations include pivoting multiple columns of data to single columns, appending data from multiple literature inventories, and merging detailed reference information and chemical ID information into the dataset.

The literature inventory was used to prioritize animal toxicological studies with exposure to the 150 PFAS for repeat dose studies of 21-day and longer durations, or with study designs focusing on exposure windows targeting reproduction or development. Studies meeting these exposure timing and duration parameters were moved forward for study evaluation (described in the next section) and endpoint-level data extraction. Animal toxicology studies not meeting these criteria did not move forward and were summarized at the literature inventory level only.

Data extraction was conducted for prioritized animal toxicology studies by two members of the evaluation team using EPA's version of Health Assessment Workspace Collaborative (HAWC) (U.S. EPA, 2021b), a free and open source web-based software application designed to manage and facilitate the process of conducting literature assessments. Data extracted included basic study information (e.g., full citation, funding, author-reported conflicts of interest); experiment details (e.g., study type, chemical name, chemical source, and purity); animal group specifics (species, strain, sex, age at exposure and assessment, husbandry); dosing regimen; endpoints evaluated; and results (qualitative or quantitative) by endpoint. Authors were not contacted for information that was not reported in a study. Data extraction was performed by one member of the evaluation team (primary extractor) and checked by a second member for completeness and accuracy (secondary extractor). Data extraction results were used to create HAWC visualizations (e.g., exposure-response arrays) by health system and effect for each PFAS chemical. The detailed HAWC extractions for animal studies are available for download from EPA HAWC in Excel format at https://hawcprd.epa.gov/assessment/100500085/downloads/ (U.S. EPA, 2020d). The data extraction output will also be available as an excel file from the Dashboard ToxValDB database in a future release.

Subsequent to HAWC data extraction, an EPA toxicologist reviewed each study to identify study-level, no-observed-adverse-effect levels [NOAELs] and lowest-observed-adverse-effect levels [LOAELs]. These judgments were made at the individual study level.

Epidemiology Studies

Epidemiological studies did not undergo full endpoint-level data extraction. A more detailed analysis of these studies, however, is being pursued as part of a separate activity (Radke et al., 2022).

Study Evaluation

Study evaluation was conducted for prioritized animal toxicological studies (≥21-day exposure durations or exposure occurring during reproduction or development) and human epidemiological studies by two reviewers using EPA's version of HAWC (U.S. EPA, 2021b). Reviews were made by toxicologists or epidemiologists with multiple years of experience in developing chemical human health assessments. During study evaluation, in each evaluation domain, at least two reviewers reached a consensus rating of *Good, Adequate, Deficient, Not Reported* or *Critically Deficient* as defined in HAWC. Key study evaluation considerations were potential sources of bias (factors affecting the magnitude or direction of an effect in systematic way) or insensitivity (factors limiting detection of a true effect). Core and prompting questions used to guide the judgment for each domain are described in more detail in the IRIS Handbook (U.S. EPA, 2020b). After a consensus rating was reached, the reviewers considered the identified strengths and limitations to reach an overall study confidence rating of High, Medium, Low, or Uninformative for each health outcome. The definitions below follow the standard template language that is used in systematic evidence maps developed by the EPA and have only been adjusted, where appropriate, for the specific needs of the PFAS 150 SEM.

- **High:** A well-conducted study with no notable deficiencies or concerns identified for the outcome(s) of interest; the potential for bias is unlikely or minimal, and the study used sensitive methodology. "High" confidence studies generally reflect judgments of good across all or most evaluation domains.

- **Medium:** A study where some deficiencies or concerns were noted for the outcome(s) of interest, but the limitations are unlikely to be of a notable degree. Generally, "medium" confidence studies will include adequate or good judgments across most domains, with the impact of any identified limitation not being judged as severe.

- **Low:** A study where one or more deficiencies or concerns were noted for the outcome(s) of interest, and the potential for bias or inadequate sensitivity could have a significant impact on the study results or their interpretation. Typically, "low" confidence studies would have a deficient evaluation for one or more domains, although some "medium" confidence studies may have a deficient rating in domain(s) considered to have less influence on the magnitude or direction of the results. Generally, in an assessment context (or a full systematic review), low confidence results are given less weight in comparison with high or medium confidence results during evidence synthesis and integration and are generally not

used as the primary sources of information for hazard identification or derivation of toxicity values unless they are the only studies available. Studies rated as low confidence only because of sensitivity concerns about biases toward the null would require additional consideration during evidence synthesis.

- **Uninformative:** A study where serious flaw(s) make the results unusable for informing hazard identification for the outcome(s) of interest. Studies with critically deficient judgments in any evaluation domain will almost always be classified as "uninformative" (see explanation above). Studies with multiple deficient judgments across domains may also be considered uninformative. As mentioned above, although outside the scope of this SEM, in an assessment or full systematic review, uninformative studies would not be considered during the synthesis and integration of evidence for hazard identification or for dose response but might be used to highlight possible research gaps. Thus, data from studies deemed uninformative are not depicted in the results displays included in this SEM.

Rationales for each study evaluation classification, including a description of how domain ratings impacted the overall study confidence rating, are available in the supplemental materials of Carlson et al. (2022) and are documented and retrievable in HAWC (https://hawcprd.epa.gov/summary/visual/assessment/100500085/animal-study-evaluation-heatmap) (U.S. EPA, 2020c).

Table A-1. Populations, Exposures, Comparators, and Outcomes (PECO) Criteria

PECO element	Description
Populations	**Human:** Any population and lifestage (occupational or general population, including children and other potentially sensitive populations). **Animal:** Nonhuman mammalian animal species (whole organism) of any lifestage (including preconception, in utero, lactation, peripubertal, and adult stages).
Exposures	**Relevant forms:** PFPrA-specific results isolated from search for ~150 PFAS chemicals + Nafion represented by ~170 PFAS structures and substances previously identified. **Human:** Any exposure to PFAS via the oral and inhalation routes because these are the most relevant routes of human exposure and typically the most useful for developing human health toxicity values. Studies are also included if biomarkers of PFAS exposure are evaluated (e.g., measured PFAS or metabolite in tissues or bodily fluids) but the exposure route is unclear or reflects multiple routes. Other exposure routes, including dermal, and mixture-only studies (i.e., without effect estimates for individual PFAS of interest) are tracked during title and abstract screening and are tagged as supplemental material. **Animal:** Any exposure to PFAS via oral or inhalation routes. Studies involving exposures to mixtures are included only if a treatment group consists of exposure to a PFAS alone. Other exposure routes, including dermal or injection, and mixture-only studies are tagged as supplemental material.
Comparators	**Human:** A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) or exposed for shorter periods of time. Worker surveillance studies are considered to meet PECO criteria, however, even if no referent group is presented. Case reports describing findings in 1–3 people in nonoccupational or occupational settings are tracked as supplemental material.

PECO element	Description
	Animal: A concurrent control group exposed to vehicle-only treatment or untreated control (control could be a baseline measurement).
Outcomes	All health outcomes (cancer and noncancer).

Table A-2. Major categories of "potentially relevant supplemental material"

Category	Description
In vitro, ex vivo, or in silico "mechanistic" studies	In vitro, ex vivo, or in silico studies reporting measurements related to a health outcome that inform the biological or chemical events associated with phenotypic effects, in both mammalian and nonmammalian model systems.
Absorption, distribution, metabolism, and excretion (ADME)	ADME studies are primarily controlled experiments where defined exposures usually occur by intravenous, oral, inhalation, or dermal routes, and the concentration of particles, a chemical, or its metabolites in blood or serum, other body tissues, or excreta are then measured. These data are used to estimate the amount absorbed (A), distributed to different organs (D), metabolized (M), and/or excreted/eliminated (E) through urine, breath, feces, etc. ADME data can also be collected from human subjects who have had environmental or workplace exposures that are not quantified or fully defined. However, to be useful, such data must involve either repeated measurements over a time period when exposure is known (e.g., is zero because previous exposure ended) or time- and subject-matched tissue or excreta concentrations (e.g., plasma and urine, or maternal and cord blood). ADME data, especially metabolism and tissue partition coefficient information, can be generated using in vitro model systems. Although in vitro data may not be as definitive as in vivo data, these studies should also be tracked as ADME. For large evidence bases it may be appropriate to separately track the in vitro ADME studies. Note: Studies describing environmental fate and transport or metabolism in bacteria are not tagged as ADME.
Classical pharmacokinetic (PK) model Studies, or physiologically based pharmacokinetic (PBPK) modeling studies	Classical PK or dosimetry modeling studies: Classical PK or dosimetry modeling usually divides the body into just one or two compartments, which are not specified by physiology, where movement of a chemical into, between, and out of the compartments is quantified empirically by fitting model parameters to ADME data. PBPK or mechanistic dosimetry modeling studies: PBPK models represent the body as various compartments (e.g., liver, lung, slowly perfused tissue, richly perfused tissue) to quantify the movement of chemicals or particles into and out of the body (compartments) by defined routes of exposure, metabolism, and elimination, and thereby estimate concentrations in blood or target tissues.
Nonmammalian model systems	Studies in nonmammalian model systems, e.g., *Xenopus* species, fish, birds, *Caenorhabditis elegans*.
Transgenic mammalian model systems	Transgenic studies in mammalian model systems.
Non-oral or non-inhalation routes of administration	Studies in which humans or animals (whole organism) were exposed via a non-oral or non-inhalation route (e.g., injection, dermal exposure).
Exposure characteristics (no health outcome assessment)	Exposure characteristic studies which include data that are unrelated to health outcomes but which provide information on exposure sources or measurement properties of the environmental agent (e.g., demonstrate a biomarker of exposure).
Mixture studies	Mixture studies that are not considered PECO-relevant because they do not contain an exposure or treatment group assessing only the chemical of interest. This category is generally used for experimental studies and generally does not apply to epidemiological studies where the exposure source may be unclear.
Case reports	Case reports describing health outcomes after exposure will be tracked as potentially relevant supplemental information when the number of subjects is three or fewer.

Category	Description
Records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials, or commentaries.
Conference abstracts	Records that do not contain sufficient documentation to support study evaluation and data extraction.
European Chemicals Agency (ECHA) read-across	Data on a nonrelevant chemical that makes inferences about a relevant PFAS chemical.
Presumed duplicate	Duplicate studies (e.g., published vs. unpublished reports) identified during data extraction and study quality evaluation.

APPENDIX B. BENCHMARK DOSE MODELING RESULTS

Modeling Procedure for Continuous Noncancer Data

Benchmark dose (BMD) modeling of continuous data is conducted with EPA's BMD Software (BMDS, Version 3.2). All continuous models available within the software are fit using a benchmark response (BMR) of 1 standard deviation (SD) relative risk or 10% extra risk when a biologically determined BMR is available (e.g., BMR of 10% relative deviation [RD] for body weight based on a biologically significant weight loss of 10%), as outlined in the Benchmark Dose Technical Guidance (U.S. EPA, 2002). A BMR of 10% RD for relative liver weights is considered a minimally biologically significant response in adult animals and was applied in this assessment for BMD modeling purposes. The default BMR of 1 SD also was applied for comparison. An adequate fit is judged on the basis of a χ^2 goodness-of-fit p-value ($p > 0.1$), the magnitude of the scaled residuals near the BMR, and a visual inspection of the model fit. In addition to these three criteria for judging adequacy of model fit, whether the variance across dose groups is homogeneous is determined. If a homogeneous variance model is deemed appropriate on the basis of the statistical test provided by BMDS (i.e., Test 2), the final BMD results are estimated from a homogeneous variance model. When the test for homogeneity of variance is rejected ($p < 0.1$), the model is rerun with the variance modeled as a power function of the mean to account for this nonhomogeneous variance. If this nonhomogeneous variance model does not adequately fit the data (i.e., Test 3; $p < 0.1$), the data set is considered unsuitable for BMD modeling. Among all models providing adequate fit, the lowest BMD lower confidence limit (BMDL) or the benchmark concentration lower confidence limit (BMCL) is selected if the BMDL or BMCL estimate from different models vary by greater than threefold. Otherwise, the BMDL or BMCL from the model with the lowest Akaike's information criterion (AIC) is selected as a potential point of departure (POD) from which to derive the oral reference dose or inhalation reference concentration (RfD or RfC).

Modeling Procedure for Dichotomous Noncancer Data

The BMD modeling of dichotomous data is conducted with the EPA's BMDS, Version 3.2. The Gamma, Logistic, Log-Logistic, Probit, Log-Probit, Hill, Multistage, and Weibull dichotomous models available within the software are fit using a BMR of 10% extra risk. In general, the BMR should be near the low end of the observable range of increased risk in the study. BMRs that are too low can result in widely disparate BMDL estimates from different models (i.e., model dependence is high). Adequacy of model fit is judged on the basis of the χ^2 goodness-of-fit p-value ($p > 0.1$), magnitude of scaled residuals (absolute value <2.0), and visual inspection of the model fit. Among all models providing adequate fit, the BMDL from the model with the lowest AIC is selected as a potential POD, if the BMDLs are sufficiently close (less than approximately threefold); if the BMDLs are not sufficiently close (greater than approximately threefold), model dependence is indicated, and the model with the lowest reliable BMDL is selected.

Model Predictions for Increased Relative Liver Weight in Male Rats (CERI, 2002c)

The procedure outlined above for continuous data was applied to the data for increased relative liver weight in adult male Crj:CD (SD) IGS (SPF) rats exposed to PFPrA for 28 days via gavage (CERI, 2002c). The BMD modeling results are summarized in Table B-1 and Figure B-1. The constant variance model provided adequate fit to the variance data, and adequate fit to the means was provided by some included models. The BMDLs for the models providing adequate fit were sufficiently close (differed by <threefold), so the model with the lowest AIC (Hill) was selected. For increased relative liver weight, the $BMDL_{10RD}$ of 6.3 mg/kg-day ($BMDL_{1SD}$ of 5.6 mg/kg-day for comparison) from this model was selected.

Table B-1. BMD Modeling Results for Increased Relative Liver Weight in Adult Male Crj:CD (SD) IGS (SPF) Rats Exposed to PFPrA for 28 Days via Gavage[a]

Model	df	χ^2 Goodness-of-Fit *p*-Value[b]	Scaled Residual at Dose Nearest BMD	AIC	BMD_{10RD} (mg/kg-d)	$BMDL_{10RD}$ (mg/kg-d)
Exponential 2	3	0.005050662	2.262925904	27.21560892	122.4887085	96.33617836
Exponential 3	3	0.005050662	2.262802575	27.2156088	122.4882507	96.3740821
Exponential 4	2	0.594805118	0.791602093	17.43812865	20.47462463	9.993505528
Exponential 5	2	0.594801226	0.79264636	17.43814174	20.5040741	9.9951759
Hill*	**2**	**0.839332468**	**0.393780633**	**16.7493825**	**14.69985034**	**6.271785406**
Polynomial 4	3	0.007285773	2.184615038	26.42770209	109.9206543	83.70900173
Polynomial 3	3	0.007285773	2.184614997	26.42770209	109.9206543	83.70900173
Polynomial 2	3	0.007285773	2.18461501	26.42770209	109.9206543	83.70900173
Power	3	0.007285773	2.184615695	26.42770209	109.9206792	83.7162667
Linear	3	0.007285773	2.184615019	26.42770209	109.9206543	83.70900173

[a]CERI (2002c).
[b]Values <0.10 failed to meet conventional goodness-of-fit criteria.
*Selected model (bold). Lowest AIC among models with adequate fit was selected (Hill).
AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the dose associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 10RD = dose associated with 10% relative deviation from the control); BMR = benchmark response; df = degree(s) of freedom.

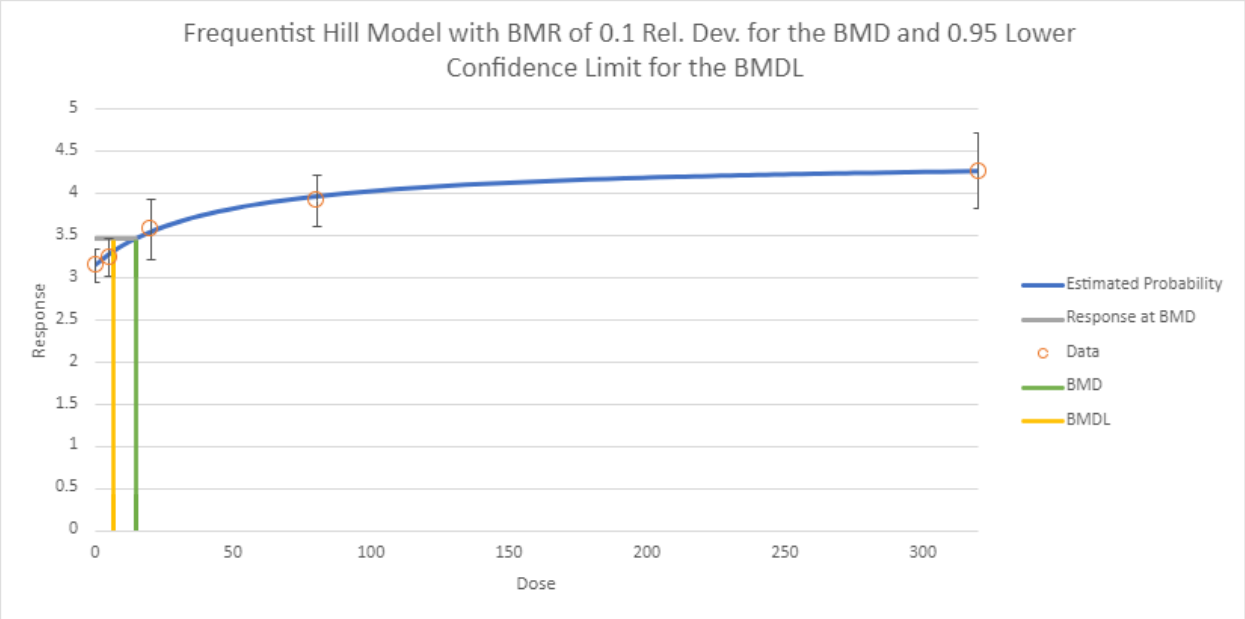

Figure B-1. Fit of Hill Model to Data for Increased Relative Liver Weight in Adult Male Crj:CD (SD) IGS (SPF) Rats Exposed to PFPrA for 28 Days via Gavage (CERI, 2002c)

BMD Model Output for Figure B-1:

Model Results

Benchmark Dose	
BMD	14.69985034
BMDL	6.271785406
BMDU	37.95628174
AIC	16.7493825
Test 4 P-value	0.839332468
D.O.F.	2

Model Parameters	
# of Parameters	5
Variable	Estimate
g	3.142501356
v	1.268335058
k	44.62975185
n	Bounded
alpha	0.078376104

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	6	3.142501356	3.15	3.15	0.27995733	0.19	0.19	0.065609467
5	6	3.270281066	3.24	3.24	0.27995733	0.21	0.21	-0.264944526
20	6	3.534993985	3.58	3.58	0.27995733	0.34	0.34	0.393780633
80	6	3.956647282	3.92	3.92	0.27995733	0.29	0.29	-0.3206458
320	6	4.255595438	4.27	4.27	0.27995733	0.43	0.43	0.126032879

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	-4.199542866	6	20.3990857
A2	-1.541134391	10	23.0822688
A3	-4.199542866	6	20.3990857
fitted	-4.37469125	4	16.7493825
R	-21.96468014	2	47.9293603

* Includes additive constant of -27.56816. This constant was not included in the LL derivation prior to BMDS 3.0.

Tests of Interest

Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	40.8470915	8	<0.0001
2	5.31681695	4	0.25630676
3	5.31681695	4	0.25630676
4	0.350296769	2	0.83933247

Model Predictions for Increased Serum Alanine Aminotransferase (ALT) in Male Rats (CERI, 2002c)

The procedure outlined above for continuous data was applied to the data for increased serum ALT in adult male Crj:CD (SD) IGS (SPF) rats exposed to PFPrA for 28 days via gavage (CERI, 2002c). The BMD modeling results are summarized in Table B-2 and Figure B-2. The constant variance model provided adequate fit to the variance data, and adequate fit to the means was provided by all included models. The BMDLs for the models providing adequate fit were not sufficiently close (differ by >threefold), so the model with the lowest BMDL (Hill) was selected. For increased serum ALT, the $BMDL_{1SD}$ of 28 mg/kg-day from this model was selected.

Table B-2. BMD Modeling Results for Increased Serum ALT in Adult Male Crj:CD (SD) IGS (SPF) Rats Exposed to PFPrA for 28 days via Gavage[a]

Model	df	χ^2 Goodness-of-Fit *p*-Value[b]	Scaled Residual at Dose Nearest BMD	AIC	BMD_{1SD} (mg/kg-d)	$BMDL_{1SD}$ (mg/kg-d)
Exponential 2	3	0.725145	0.495322432	166.1551966	137.6285	103.6144
Exponential 3	3	0.7251452	0.495266835	166.1551956	137.6445	103.6143
Exponential 4	2	0.6611853	−0.108470434	167.6658274	86.36887	34.31788
Exponential 5	2	0.6611853	−0.108457685	167.6658274	86.36948	34.31813
Hill*	**2**	**0.6635677**	**−0.118454015**	**167.6586338**	**85.62671**	**28.43509**
Polynomial 4	3	0.7661823	0.379605768	165.9835564	124.7527	90.53213
Polynomial 3	3	0.7661823	0.379605711	165.9835564	124.7527	90.53213
Polynomial 2	3	0.7661823	0.3796057	165.9835564	124.7527	90.53213
Power	3	0.7661823	0.379605707	165.9835564	124.7526	90.53205
Linear	3	0.7661823	0.379605721	165.9835564	124.7527	90.53213

[a]CERI (2002c).
[b]Values <0.10 failed to meet conventional goodness-of-fit criteria.
*Selected model (bold). Lowest AIC among models with adequate fit was selected (Hill).
AIC = Akaike's information criterion; ALT = alanine aminotransferase; BMD = maximum likelihood estimates of the dose associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 1SD = dose associated with 1 standard deviation relative risk from the control); BMR = benchmark response; df = degree(s) of freedom.

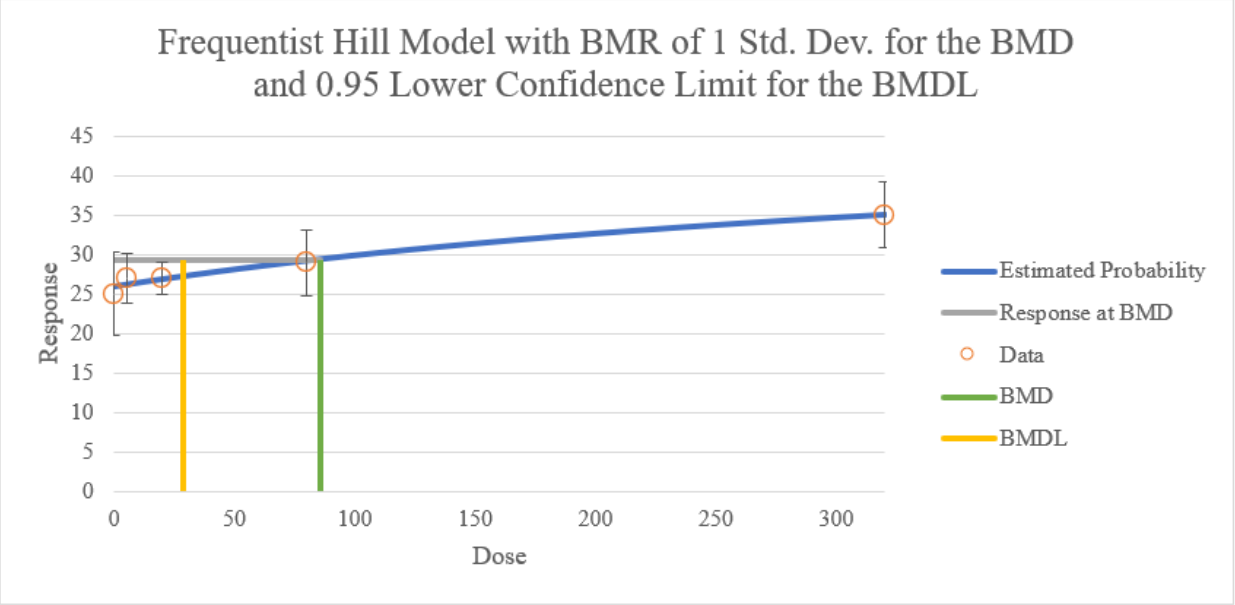

Figure B-2. Fit of Hill Model to Data for Increased Serum ALT in Adult Male Crj:CD (SD) IGS (SPF) Rats Exposed to PFPrA for 28 days via Gavage (CERI, 2002c)

BMD Model Output for Figure B-2:

Model Results

Benchmark Dose	
BMD	85.62671486
BMDL	28.43508564
BMDU	239.4949956
AIC	167.6586338
Test 4 *p*-value	0.66356774
df	2

Model Parameters	
# of Parameters	5
Variable	Estimate
g	25.89898576
v	22.30697177
k	465.9927831
n	Bounded
alpha	11.99003863

Goodness of Fit

Dose	Size	Estimated Median	Calc'd. Median	Observed Mean	Estimated SD	Calc'd. SD	Observed SD	Scaled Residual
0	6	25.89898576	25	25	3.46266352	5	5	−0.635942931
5	6	26.13579376	27	27	3.46266352	3	3	0.611339889
20	6	26.81698177	27	27	3.46266352	2	2	0.129467182
80	6	29.16744973	29	29	3.46266352	4	4	−0.118454015
320	6	34.98078793	35	35	3.46266352	4	4	0.013590628

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	−79.41919259	6	170.838385
A2	−76.87604927	10	173.752099
A3	−79.41919259	6	170.838385
fitted	−79.82931692	4	167.658634
R	−89.92741703	2	183.854834

*Includes additive constant of −27.56816. This constant was not included in the log likelihood derivation prior to BMDS 3.0.

Tests of Interest

Test	−2*Log(Likelihood Ratio)	Test df	*p*-value
1	26.10273551	8	0.00100861
2	5.08628663	4	0.27855798
3	5.08628663	4	0.27855798
4	0.82024867	2	0.66356774

Model Predictions for Increased Serum Alkaline Phosphatase (ALP) in Male Rats (CERI, 2002c)

The procedure outlined above for continuous data was applied to the data for increased serum ALP in adult male Crj:CD (SD) IGS (SPF) rats exposed to PFPrA for 28 days via gavage (CERI, 2002c). The BMD modeling results are summarized in Table B-3 and Figure B-3. The constant variance model provided adequate fit to the variance data, and adequate fit to the means was provided by some included models. The BMDLs for the models providing adequate fit were sufficiently close (differed by <threefold), so the model with the lowest AIC (Exponential Degree 5) was selected. For increased serum ALP, the $BMDL_{1SD}$ of 20 mg/kg-day from this model was selected.

Table B-3. BMD Modeling Results for Increased Serum ALP in Adult Male Crj:CD (SD) IGS (SPF) Rats Exposed to PFPrA for 28 Days via Gavage[a]

Model	df	χ^2 Goodness-of-Fit *p*-Value[b]	Scaled Residual at Dose Nearest BMD	AIC	BMD_{1SD} (mg/kg-d)	$BMDL_{1SD}$ (mg/kg-d)
Exponential 2	3	0.0473274	−0.467410275	356.8601623	298.0884	180.9615
Exponential 3	3	0.0473274	−0.467408907	356.8601623	298.0878	180.9639
Exponential 4	2	0.2900059	−1.0137466	353.3986597	41.09192	13.77903
Exponential 5*	**2**	**0.5081367**	**0.446996822**	**353.3608541**	**67.12098**	**20.33889**
Hill	2	0.5081348	−0.001142051	353.3608582	34.13729	20.52392
Polynomial 4	3	0.0516934	−0.53163545	356.663328	284.0054	163.4765
Polynomial 3	3	0.0516934	−0.53163533	356.663328	284.0054	163.4765
Polynomial 2	3	0.0516934	−0.531635319	356.663328	284.0054	163.4765
Power	3	0.0516934	−0.531635379	356.663328	284.0054	163.479
Linear	3	0.0516934	−0.531635714	356.663328	284.0054	163.4765

[a]CERI (2002c).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
*Selected model (bold). Lowest AIC among models with adequate fit was selected (Exponential 5).
AIC = Akaike's information criterion; ALP = alkaline phosphatase; BMD = maximum likelihood estimates of the dose associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 1SD = 1 dose associated with 1 standard deviation relative risk from the control); BMR = benchmark response; df = degree(s) of freedom.

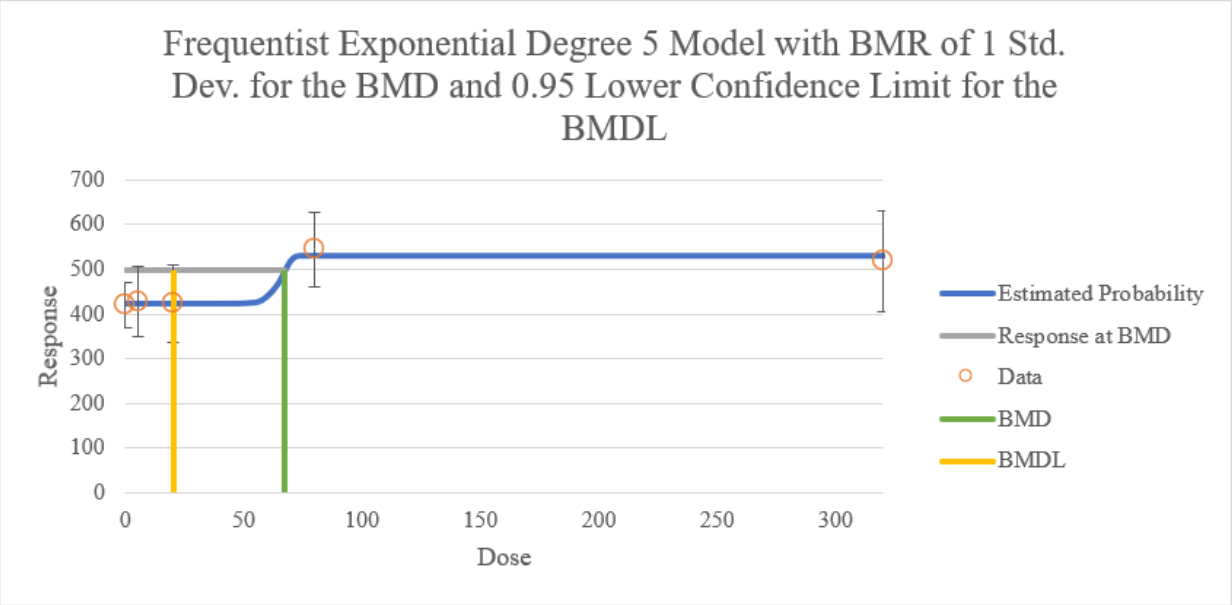

Figure B-3. Fit of Exponential Degree 5 Model to Data for Increased Serum ALP in Adult Male Crj:CD (SD) IGS (SPF) Rats Exposed to PFPrA for 28 Days via Gavage (CERI, 2002c)

BMD Model Output for Figure B-3:

Model Results

Benchmark Dose	
BMD	67.12097645
BMDL	20.33888677
BMDU	Infinity
AIC	353.3608541
Test 4 *p*-value	0.508136728
df	1

Model Parameters	
# of Parameters	5
Variable	Estimate
a	423.9999997
b	0.015025569
c	1.253538871
d	17.99993883
log-alpha	8.607475193

Goodness of Fit

Dose	Size	Estimated Median	Calc'd. Median	Observed Mean	Estimated SD	Calc'd. SD	Observed SD	Scaled Residual
0	6	423.9999997	420	420	73.9757692	48	48	−0.132448211
5	6	423.9999997	428	428	73.9757692	74	74	0.132448229
20	6	423.9999998	424	424	73.9757692	83	83	7.75705E−09
80	6	531.5004808	545	545	73.9757692	79	79	0.446996822
320	6	531.5004808	518	518	73.9757692	107	107	−0.447028664

Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	−171.461476	6	354.922952
A2	−169.651633	10	359.303266
A3	−171.461476	6	354.922952
fitted	−171.6804271	5	353.360854
R	−177.8303481	2	359.660696

* Includes additive constant of −27.56816. This constant was not included in the log likelihood derivation prior to BMDS 3.0.

Tests of Interest

Test	−2*Log(Like-lihood Ratio)	Test df	*p*-value
1	16.35743003	8	0.03754072
2	3.619685881	4	0.45991465
3	3.619685881	4	0.45991465
4	0.437902174	1	0.50813673

Model Predictions for Increased Hepatocyte Hypertrophy in Male Rats (CERI, 2002c)

The procedure outlined above for dichotomous data was applied to the data for increased hepatocyte hypertrophy in adult male Crj:CD (SD) IGS (SPF) rats exposed to PFPrA for 28 days via gavage (CERI, 2002c). The BMD modeling results are summarized in Table B-4 and Figure B-4. All models provided adequate fit (p-value > 0.10). The BMDLs for the models providing adequate fit were not sufficiently close (differed by >threefold), so the model with the lowest BMDL (Multistage Degree 1) was selected. For increased hepatocyte hypertrophy, the $BMDL_{10ER}$ of 7.9 mg/kg-day from this model was selected.

Table B-4. BMD Modeling Results for Increased Hepatocyte Hypertrophy in Adult Male Crj:CD (SD) IGS (SPF) Rats Exposed to PFPrA for 28 Days via Gavage[a]

Model	df	χ^2 Goodness-of-Fit p-Value[b]	Scaled Residual at Dose Nearest BMD	AIC	BMD_{10ER} (mg/kg-d)	$BMDL_{0.1ER}$ (mg/kg-d)
Dichotomous Hill	1	0.9994976	2.89723E−06	13.63817081	71.52739	22.82469
Gamma	1	0.9904814	0.000386722	13.63845452	60.62737	16.55655
Log-Logistic	3	1	−7.48247E−10	9.638170614	71.55622	22.82473
Multistage 3	3	0.9980426	0.026748569	9.713472066	51.37595	12.69572
Multistage 2	3	0.9833786	−0.384943695	9.957035722	41.5625	12.92712
Multistage 1*	2	**0.3982919**	**−0.950683507**	**14.89786409**	**15.01799**	**7.890077**
Weibull	3	0.9997399	0.013825013	9.657704573	57.16347	15.74647
Logistic	3	1	1.48722E−06	9.638184036	73.04749	31.07119
Log-Probit	2	0.9999999	5.62727E−08	11.63817039	69.91623	22.30673
Probit	3	0.9999977	0.000912285	9.63902246	64.88286	28.34315

[a]CERI (2002c).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
*Selected model (bold). Lowest AIC among models with adequate fit was selected (Hill).
AIC = Akaike's information criterion; ALP = alkaline phosphatase; BMD = maximum likelihood estimate of the dose associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 10ER = dose associated with 10% extra risk from the control); BMR = benchmark response; df = degree(s) of freedom.

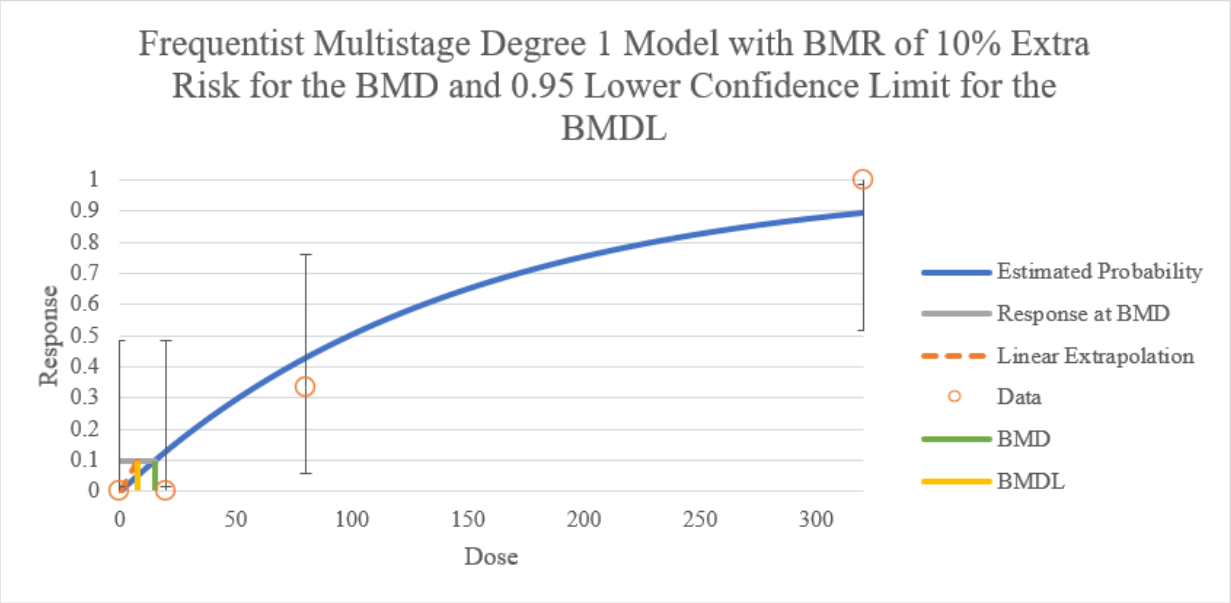

Figure B-4. Fit of Multistage Degree 1 Model to Data for Increased Serum ALP in Adult Male Crj:CD (SD) IGS (SPF) Rats Exposed to PFPrA for 28 Days via Gavage (CERI, 2002c)

BMD Model Output for Figure B-4:

Model Results

Benchmark Dose	
BMD	15.01799345
BMDL	7.890076616
BMDU	30.73698127
AIC	14.89786409
p-value	0.398291862
df	2
Chi^2	1.841140441
Slope Factor	0.012674148

Model Parameters	
# of Parameters	2
Variable	Estimate
g	1.55762E−08
b1	0.007015619

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.55762E−08	9.34574E−08	0	6	−0.0003057
20	0.130913301	0.785479804	0	6	−0.9506835
80	0.429504223	2.577025336	2	6	−0.475893
320	0.894072248	5.364433486	6	6	0.8431293

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	*p*-Value
Full Model	−3.81908501	4	–	–	NA
Fitted Model	−5.448932047	2	3.25969407	2	0.1959595
Reduced Model	−15.27634004	1	22.9145101	3	<0.0001