United States Environmental Protection Agency

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Human Health Toxicity Values for Perfluorobutane Sulfonic Acid (CASRN 375-73-5) and Related Compound Potassium Perfluorobutane Sulfonate (CASRN 29420-49-3)

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U.S. Environmental Protection Agency
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PREFACE

This assessment titled *Human Health Toxicity Values for Perfluorobutane Sulfonic Acid and Related Compound Potassium Perfluorobutane Sulfonate* is a toxicity assessment developed by the U.S. EPA's Office of Research and Development (ORD) Center for Public Health and Environmental Assessment (CPHEA).

The perfluorobutane sulfonic acid (PFBS) toxicity assessment is one of the key goals of the Agency's [HYPERLINK "https://www.epa.gov/pfas/epas-pfas-action-plan"] and provides qualitative and quantitative toxicity information that can be used along with exposure information and other important considerations to assess potential health risks to determine if, and when, it is appropriate to take action to address this chemical. Similar to assessments developed under U.S. EPA's Integrated Risk Information System (IRIS), this assessment is available for use across multiple U.S. EPA program and regional offices, other federal agencies, states, tribes, external stakeholders, and other entities as needed. One use of this assessment is to update and replace the existing 2014 Provisional Peer-Reviewed Toxicity Value (PPRTV) assessment for PFBS used by the U.S. EPA's Superfund Program.

The PFBS human health toxicity values presented in this assessment were developed based on the best available science. The assessment provides high-quality evaluations and conclusions drawn from publicly available information on the toxicity of PFBS. This assessment is not a regulation; rather, it provides a critical part of the scientific foundation for risk assessment decision making. The PFBS assessment provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users, including risk assessors and risk managers, are advised to review the information, including potential uncertainties, provided in this document to ensure that the assessment is appropriate for the circumstances (e.g., exposure pathways, concentrations, presence of sensitive subpopulations) in question and the risk management decisions that would be supported by the risk assessment.

The PFBS toxicity assessment underwent a rigorous and thorough development and review process, as described below.

<u>Overview of major steps in the PFBS assessment development and review process</u>

- Draft assessment development
- Review by U.S. EPA program and regional offices (i.e., Agency review)
- Review by other federal agencies (i.e., interagency review)
- External peer review
- Public comment period
- Second external peer review
- Agency and interagency review

This assessment was provided for review to scientists in U.S. EPA's program and regional offices in the early and late stages of the assessment process. Comments were submitted by:

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Office of the Administrator/Office of Children's Health Protection
Office of the Administrator/Office of Policy
Office of Chemical Safety and Pollution Prevention
Office of Land and Emergency Management
Office of Research and Development
Office of Water
Region 2, New York, NY
Region 3, Boston, MA
Region 4, Atlanta, GA
Region 5, Chicago, IL
Region 8, Denver, CO

This assessment was provided for review to other federal agencies in the early and late stages of the assessment process. Representatives from federal agencies and from the Environmental Council of the States (ECOS) were briefed during the assessment scoping and draft development process on March 9, 2018; May 2, 2018; and August 27, 2018. In the latter stages, this interagency review was conducted through the oversight of the Office of Management and Budget's PFAS Technical Working Group (TWG). Comments were submitted by:

Department of Defense
Department of Health and Human Services/Agency for Toxic Substances and Disease Registry
Food and Drug Administration
National Institute of Environmental Health Sciences/National Toxicology Program
National Institute of Occupational Safety and Health
National Aeronautics and Space Administration
Executive Office of the President/Office of Management and Budget

This assessment was peer reviewed by independent, expert scientists external to U.S. EPA before and after the public comment period. The reports of the two external peer reviews of the U.S. EPA's draft Human Health Toxicity Values for PFBS, dated November 2018 and October 2020, are available at [HYPERLINK "https://www.epa.gov/pfas/genx-and-pfbs-draft-toxicity-assessments"]. Comments from external peer review were submitted by:

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This assessment was released for public comment from November 21, 2018 to January 22, 2019. The public comments are available on [HYPERLINK "http://www.regulations.gov"] in the Docket ID No. EPA-HQ-OW-2018-0614.

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COMMONLY USED ABBREVIATIONS AND ACRONYMS

AEC	absolute eosinophil count
AFFF	aqueous film-forming foam
AIC	Akaike's information criterion
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
BW	body weight
CA	chromosomal aberration
CASRN	Chemical Abstracts Service registry number
CHO	Chinese hamster ovary (cell line)
CI	confidence interval
CPHEA	Center for Public Health and Environmental Assessment
CPN	chronic progressive nephropathy
D3	deiodinase 3
DAF	dosimetric adjustment factor
DNA	deoxyribonucleic acid
ECP	eosinophilic cationic protein
GD	gestation day
GLP	Good Laboratory Practice
HAWC	Health Assessment Workspace Collaborative
HED	human equivalent dose
HPT	hypothalamic-pituitary-thyroid
i.v.	intravenous
ICR	Institute of Cancer Research
K^+PFBS	potassium perfluorobutane sulfonate
k_{elim}	serum elimination rate constant
LD	lactation day
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MW	molecular weight
NHANES	National Health and Nutrition Examination Survey
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
NZW	New Zealand White (rabbit breed)
OR	odds ratio
PECO	Population, Exposure, Comparator, and Outcome
PFAA	perfluoroalkyl acid
PFAS	per- and polyfluoroalkyl substances
PFBS	perfluorobutane sulfonic acid
PFHxA	perfluorohexanoic acid
PFOA	perfluorooctanoic acid
PFOS	perfluorooctane sulfonic acid
PND	postnatal day
POD	point of departure
RfC	inhalation reference concentration
RfD	oral reference dose
ROS	reactive oxygen species
rT_3	reverse triiodothyronine
S-D	Sprague-Dawley
SD	standard deviation
T_2	3,5-diiodo-L-thyronine
T_3	triiodothyronine
T_4	thyroxine
TBG	thyroid-binding globulin
TSH	thyroid-stimulating hormone
TTR	transthyretin
UF	uncertainty factor
UF_A	interspecies uncertainty factor
UFc	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. EPA	U.S. Environmental Protection Agency
VLDL	very low-density lipoprotein

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EXECUTIVE SUMMARY

SUMMARY OF OCCURRENCE AND HEALTH EFFECTS

The U.S. Environmental Protection Agency (U.S. EPA) is issuing draft subchronic and chronic oral toxicity values for perfluorobutane sulfonic acid (PFBS) (Chemical Abstracts Service registry number [CASRN] 375-73-5) and its related salt, potassium perfluorobutane sulfonate (K^+PFBS) (CASRN 29420-49-3). The ionic state of per- and polyfluoroalkyl substances (PFAS) such as PFBS influence physicochemical properties such as water or lipid solubility and bioaccumulative potential, which in turn impact fate and transport in the environment and potential human health and ecological effects in exposed populations. K^+PFBS fully dissociates in aqueous solutions with pH levels ranging from 4–9; thus, the oral toxicity values derived in this document are also applicable to the deprotonated anionic form of PFBS (i.e., $PFBS^-$; CASRN 45187-15-3).

The toxicity assessment for PFBS includes toxicity values associated with potential noncancer health effects following oral exposure (in this case, oral reference doses [RfDs]). This assessment evaluates human health hazards. The toxicity assessment and the values contained within is not a risk assessment because it does not include an exposure assessment nor an overall risk characterization. Further, the toxicity assessment does not address the legal, political, social, economic, or technical considerations involved in risk management. When final, the PFBS toxicity assessment can be used by U.S. EPA, states, tribes, and local communities, along with specific exposure and other relevant information, to determine, under the appropriate regulations and statutes, if, and when, it is necessary to take action to address potential risk associated with human exposures to PFBS.

PFBS and K^+PFBS are both four-carbon, fully fluorinated alkane members of a large and diverse class of linear and branched compounds known as "per- and polyfluoroalkyl substances," or PFAS. In the early 2000s, concerns grew over the environmental persistence, bioaccumulation potential, and long half-lives in humans of longer chain PFAS, in particular, perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS). As a result, shorter chain PFAS such as PFBS were developed and integrated into various consumer products and industrial applications, because PFBS has the desired properties and characteristics associated with this class of compounds but with faster elimination from the body than PFOA and PFOS. PFBS is associated with aqueous film-forming foam (foams (AFFFs) and used during chrome electroplating as a mist suppressant. It has also been found in food contact materials, dust, and source and finished drinking water. Accordingly, oral intake of water and food, inhalation, and dermal contact are plausible modes of PFBS exposure, with the oral route being the primary route of exposure. PFBS has been detected in human urine, confirming exposure to this PFAS; however, the magnitude of human exposure likely depends on factors such as occupation (e.g., processing and/or manufacture of PFBS or PFBS-containing products and chrome electroplating) and living conditions (e.g., proximity to locations that make or use PFBS-containing products and nearby well-water use).

Human studies have examined possible associations between PFBS exposure and potential health outcomes such as alteration of menstruation, reproductive hormones or semen parameters, kidney function (uric acid production), lung function (induction of asthma), and lipid

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profile. The ability to draw conclusions about associations is limited due to the small number of human studies per outcome. Of the examined health outcomes, only asthma and serum cholesterol levels in humans were found to exhibit a statistically significant positive association with PFBS exposure. No studies have been identified that evaluate the association between PFBS exposure and potential cancer outcomes. While the epidemiology studies were not influential to drawing evidence integration judgments or the derivation of toxicity values, the general findings identify potential areas of future research.

Animal studies of repeated-dose PFBS exposure have been exclusively via the oral route, used the potassium salt of PFBS (K^+PFBS) as the source exposure material, and have examined noncancer effects only. The available rat and mouse studies support identification of thyroid, developmental, and kidney endpoints as potential health effects following repeated exposures in utero and/or during adulthood. Animal studies have also evaluated other health outcomes, such as liver effects, reproductive parameters, lipid/lipoprotein homeostasis, and effects on the spleen and hematology; however, the available evidence does not support a clear association with PFBS exposure and these outcomes.

Noncancer Effects Observed Following Oral Exposure

Oral exposures to PFBS or its K^+ salt in adult and developing rats and mice have been shown to result in thyroid, developmental, and kidney effects. Thyroid effects in exposed adult rats and mice and in developing mice were primarily expressed through significant decreases in circulating levels of hormones such as thyroxine (T_4) and triiodothyronine (T_3). In early developmental life stages in mice (e.g., newborn), decreases in thyroid hormone were accompanied by other effects indicative of delayed maturation or reproductive development (e.g., vaginal patency and eyes opening). Kidney weight and/or histopathological alterations (e.g., renal tubular and ductal epithelial hyperplasia) were observed in rats following short-term and subchronic oral exposures. Many of the kidney effects, however, occurred at higher doses than did the thyroid and developmental effects. The limited number of human studies examining oral PFBS exposure does not inform the potential for effects in thyroid, developing offspring, or the renal system.

Oral Reference Doses for Noncancer Effects

Subchronic[1] and chronic[2] oral RfDs were derived for PFBS. The hazards of potential concern include thyroid, developmental, and kidney effects. From these identified targets of PFBS toxicity, perturbation of thyroid hormone levels (e.g., T_4) was used as the critical effect for deriving a subchronic and chronic RfD. Based on recommendations in the U.S. EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2011</Year><RecNum>1311</RecNum><IDText>752972</IDText><Dis

[1]Subchronic exposure: Repeated exposure by the oral, dermal, or inhalation route for more than 30 days, up to approximately 10% of the lifespan in humans (more than 30 days up to approximately 90 days in typically used laboratory animal species).

[2]Chronic exposure: Repeated exposure by the oral, dermal, or inhalation route for more than approximately 10% of the lifespan in humans (more than approximately 90 days to 2 years in typically used laboratory animal species). ([HYPERLINK "https://ofmpub.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do?details=&glossaryName=IRIS%20Glossary" \l "formTop"])

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playText>(U.S. EPA, 2011b)</DisplayText><record><rec-number>1311</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1311</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Recommended use of body weight 3/4 as the default method in derivation of the oral reference dose</title></titles><pages>1-50</pages><dates><year>2011</year></dates><pub-location>Washington, DC</pub-location><publisher>U.S. Environmental Protection Agency, Risk Assessment Forum, Office of the Science Advisor</publisher><isbn>EPA/100/R-11/0001</isbn><label>752972</label><urls><related-urls><url>https://www.epa.gov/sites/production/files/2013-09/documents/recommended-use-of-bw34.pdf</url></related-urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>], chemical-specific toxicokinetic data (e.g., serum half-lives) were used to scale a toxicologically equivalent dose of orally administered PFBS from animals to humans. Following the U.S. EPA's *Benchmark Dose Technical Guidance Document* [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2012</Year><RecNum>1309</RecNum><IDText>1239433</IDText><DisplayText>(U.S. EPA, 2012)</DisplayText><record><rec-number>1309</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1309</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Benchmark dose technical guidance</title></titles><dates><year>2012</year></dates><pub-location>Washington, DC</pub-location><publisher>U.S. Environmental Protection Agency, Risk Assessment Forum</publisher><isbn>EPA/100/R-12/001</isbn><label>1239433</label><urls><related-urls><url>https://www.epa.gov/risk/benchmark-dose-technical-guidance</url></related-urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>], benchmark dose (BMD) modeling of thyroid effects in a developmental life stage following exposure to K^+PFBS in utero resulted in a $BMDL_{0.5SD}$ human equivalent dose (HED) of 0.16 milligrams per kilogram per day (mg/kg-day). This HED associated with thyroid effects served as the point of departure (POD) for deriving the subchronic and chronic RfDs.

The subchronic RfD for K^+PFBS was calculated by dividing the POD (HED) for decreased serum total T_4 observed in newborn (Postnatal Day [PND] 1) mice, in the study conducted by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"], by a composite uncertainty factor (UF_C) of 100 to account for extrapolation from mice to humans (an interspecies uncertainty factor, or UF_A, of 3), for interindividual differences in human susceptibility (intraspecies uncertainty factor, or UF_H, of 10), and for deficiencies in the toxicity database (database uncertainty factor, or UF_D, of 3) (a value of 1 was applied for subchronic-to-chronic UF, or UF_S, and LOAEL-to-NOAEL uncertainty factor, or UF_L) (see [REF _Ref55817965 \h]), yielding a subchronic RfD of 0.0016 mg/kg-day rounded to 2×10^{-3} mg/kg-day. Because K^+PFBS is fully dissociated in water at the environmental pH range of 4–9 to the PFBS anion ($PFBS^-$) and the K^+ cation, data for K^+PFBS were used to derive

a subchronic RfD for the free acid (PFBS) by adjusting for differences in molecular weight (MW) between K^+PFBS (338.19) and PFBS (300.10), yielding the value of 0.0014 mg/kg-day rounded to 1×10^{-3} mg/kg-day for the subchronic RfD for PFBS (free acid).

The chronic RfD for K^+PFBS associated with thyroid effects was calculated by dividing the POD (HED) for decreased serum total T_4 observed in newborn (PND 1) mice, in the study conducted by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"], by a UF_C of 300 to account for extrapolation from mice to humans (UF_A of 3), for interindividual differences in human susceptibility (UF_H of 10), and deficiencies in the toxicity database (UF_D of 10) (a value of 1 was applied for UF_S and UF_L) (see [REF _Ref55817975 \h]), yielding a chronic RfD of 0.00053 mg/kg-day rounded to 5×10^{-4} mg/kg-day. Like the subchronic RfD for thyroid effect, based on the data for K^+PFBS, a chronic RfD for PFBS (free acid) of 0.00047 mg/kg-day rounded to 5×10^{-4} mg/kg-day was derived.

Confidence in the Oral RfDs

The overall confidence in the subchronic RfD for thyroid effects is medium. The gestational exposure study conducted by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"] reported administration of K^+PFBS by gavage in pregnant Institute of Cancer Research (ICR) mice (10/dose) from Gestation Days (GDs) 1 to 20. This study was of good quality (i.e., high confidence) with adequate reporting and consideration of appropriate study design, methods, and conduct (click to see [HYPERLINK "https://hawcprd.epa.gov/rob/study/100000968/"] in HAWC[3]). Confidence in the oral toxicity database for derivation of the subchronic RfD is medium because, although there are multiple short-term studies and a subchronic-duration toxicity study in laboratory animals, a two-generation reproductive toxicity study in rats [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1044</RecNum><IDText>1578545</IDText><DisplayText>(Lieder et al., 2009b)</DisplayText><record><rec-number>1044</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1044</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lieder, P. H.</author><author>York, R. G.</author><author>Hakes, D. C.</author><author>Chang, S. C.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>A two-generation oral gavage reproduction study with potassium perfluorobutanesulfonate (K+PFBS) in Sprague Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>33-45</pages><volume>259</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>19428941</accession-num><label>1578545</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2009.01.027</url></related-urls></urls><electronic-

[3]HAWC: A modular web-based interface to facilitate development of human health assessments of chemicals; see Appendix D for details.

resource-num>10.1016/j.tox.2009.01.027</electronic-resource-num><language>English</language></record></Cite></EndNote>], and multiple developmental toxicity studies in mice and rats, there are no PFBS studies available that have specifically evaluated health effect domains of emerging concern across the PFAS class such as immunotoxicity and mammary gland development [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Further, neurodevelopmental effects are of particular concern when perturbations in thyroid hormone occur during a sensitive early life stage, and the absence of a study evaluating neurodevelopmental effects following PFBS exposure is a source of uncertainty in the assessment.

The overall confidence in the chronic RfD for thyroid effects is low. Although the chronic RfD, like the subchronic RfD, was derived using data from the high-confidence principal study conducted by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"], there is increased concern about the potential for identification of hazards following longer (i.e., chronic) duration PFBS exposures. In addition, because of the lack of studies that specifically evaluated health effect domains of emerging concern across the PFAS class, such as immunotoxicity, mammary gland development, or neurodevelopmental at any exposure duration—but particularly for chronic duration—confidence in the database specifically for a chronic RfD is low.

Effects Other Than Cancer Observed Following Inhalation Exposure

There are no studies available that examined toxicity in humans or experimental animals following inhalation exposure, thereby precluding the derivation of an inhalation reference concentration (RfC).

Evidence for Carcinogenicity

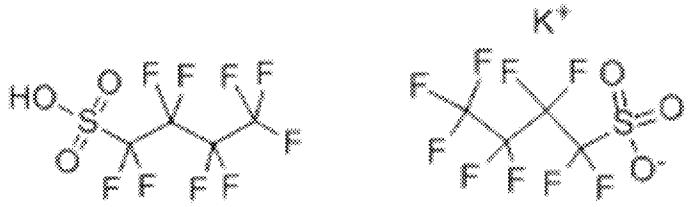
Under the U.S. EPA's *Guidelines for Carcinogen Risk Assessment* [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2005</Year><RecNum>1222</RecNum><IDText>6324329</IDText><DisplayText>(U.S. EPA, 2005)</DisplayText><record><rec-number>1222</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1222</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Guidelines for carcinogen risk assessment</title></titles><dates><year>2005</year></dates><pub-location>Washington, DC</pub-location><publisher>U.S. Environmental Protection Agency, Risk Assessment Forum</publisher><isbn>EPA/630/P-03/001B</isbn><label>6324329</label><work-type>EPA Report</work-type><urls><related-urls><url>https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf</url></related-urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>], the Agency concluded that there is *"Inadequate Information to Assess Carcinogenic Potential"* for PFBS and K^+PFBS by either oral or inhalation routes of exposure. Therefore, the lack of data on the carcinogenicity of PFBS and the related compound K^+PFBS precludes the derivation of quantitative estimates for either oral (oral slope factor) or inhalation (inhalation unit risk) exposure.

1.0 BACKGROUND

1.1 PHYSICAL AND CHEMICAL PROPERTIES

Perfluorobutane sulfonic acid (PFBS) (Chemical Abstracts Service registry number [CASRN] 375-73-5)[4] and its related salt, potassium perfluorobutane sulfonate (K^+PFBS) (CASRN 29420-49-3), are members of the group of per- and polyfluoroalkyl substances (PFAS), more specifically the short-chain perfluoroalkane sulfonates. For purposes of this assessment, "PFBS" will signify the ion, acid, or any salt of PFBS. Concerns about PFBS and other PFAS stem from the resistance of these compounds to hydrolysis, photolysis, and biodegradation, which leads to their persistence in the environment [ADDIN EN.CITE <EndNote><Cite><Author>Sundström</Author><Year>2012</Year><RecNum>796</RecNum><IDText>1784738</IDText><DisplayText>(Sundström et al., 2012)</DisplayText><record><rec-number>796</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">796</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Sundström, M.</author><author>Bogdanska, J.</author><author>Pham, H. V.</author><author>Athanasios, V.</author><author>Nobel, S.</author><author>McAlees, A.</author><author>Eriksson, J.</author><author>Depierre, J. W.</author><author>Bergman, Å.</author></authors></contributors><titles><title>Radiosynthesis of perfluorooctanesulfonate (PFOS) and perfluorobutanesulfonate (PFBS), including solubility, partition and adhesion studies</title><secondary-title>Chemosphere</secondary-title><alt-title>Chemosphere</alt-title><short-title>Chemosphere</short-title></titles><periodical><full-title>Chemosphere</full-title><abbr-1>Chemosphere</abbr-1></periodical><alt-periodical><full-title>Chemosphere</full-title><abbr-1>Chemosphere</abbr-1></alt-periodical><pages>865-871</pages><volume>87</volume><number>8</number><dates><year>2012</year></dates><isbn>ISSN 0045-6535
EISSN 1879-1298</isbn><accession-num>22336737</accession-num><label>1784738</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.chemosphere.2012.01.027</url></related-urls></urls><electronic-resource-num>10.1016/j.chemosphere.2012.01.027</electronic-resource-num><language>English</language></record></Cite></EndNote>]. The chemical formula of PFBS is $C_4HF_9O_3S$ and the chemical formula of K^+PFBS is $C_4F_9KO_3S$. Their respective chemical structures are presented in [REF _Ref55818884 \h]. K^+PFBS differs from PFBS by being associated with a potassium ion. The reported water solubility of each species suggests that in aqueous environments the sulfonate would be the predominant form. The preferential use of K^+PFBS in laboratory studies is related to the optimal dissociation of the salt to the sulfonate (i.e., $PFBS^-$) at pH values ranging from 4 to 9 (see [REF _Ref55817989 \h]). [REF _Ref55817989 \h] provides a list of the physicochemical properties for PFBS and K^+PFBS.

[4]The CASRN given is for linear PFBS; the source PFBS used in toxicity studies was assayed at ≥98% linear, suggesting some minor proportion of other chemicals, such as branched PFBS isomers, are present. Thus, observed health effects may apply to the total linear and branched isomers in a given exposure source.



PFBS **K⁺PFBS**

Figure [SEQ Figure * ARABIC]. PFBS and K^+PFBS Chemical Structures

Table [SEQ Table * ARABIC]. Physicochemical Properties of PFBS (CASRN 375-73-5) and Related Compound K^+PFBS (CASRN 29420-49-3)

Property (unit)	Value[a]	
	PFBS (free acid)[b]	K^+PFBS (potassium salt)[c]
Boiling point (°C)	152	447
Density (g/cm^3)	1.83 (predicted)	1.83 (predicted)
Vapor pressure (mm Hg)	0.104 (predicted)	1.12×10^{-8}
pH	ND	ND
Solubility in water (mol/L)	0.0017	0.08
Molecular weight (g/mol)	300.09	338.18
Dissociation constant	NA	Fully dissociated in water over the pH range of 4–9

[a]Values are experimentally determined unless otherwise indicated.
[b][HYPERLINK "https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID5030030"].
[c][HYPERLINK "https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID3037707"].

K^+PFBS = potassium perfluorobutane sulfonate; NA = not applicable; ND = no data; PFBS = perfluorobutane sulfonic acid.

1.2 OCCURRENCE

PFBS-based compounds are surfactants used primarily in the manufacture of paints, cleaning agents, and water- and stain-repellent products and coatings. They serve as replacements for perfluorooctane sulfonic acid (PFOS) [ADDIN EN.CITE <EndNote><Cite><Author>3M</Author><Year>2002</Year><RecNum>1246</RecNum><IDText>4339178</IDText><DisplayText>(3M, 2002b)</DisplayText><record><rec-number>1246</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1246</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>3M,</author></authors></contributors><titles><title>Environmental, health, safety, and regulatory (EHSR) profile of perfluorobutane sulfonate (PFBS)</title></titles><dates><year>2002</year></dates><label>4339178</label><urls><related-urls><url>: http://multimedia.3m.com/mws/media/172303O/ehsr-profile-of-perfluorobutane-sulfonate-pfbs.pdf</url></related-urls></urls><language>English</language><modified-date>3M Company</modified-date></record></Cite></EndNote>]. Various sources report detection or occurrence in environmental media and consumer products, including drinking water, ambient water, dust, carpeting and carpet cleaners, floor wax, and food packaging.

Oral exposure via drinking water might be expected in areas where contamination has been reported. U.S. EPA Unregulated Contaminant Monitoring Rule data for public drinking water utilities in 2013–2015 showed levels of PFBS above the minimum reporting level (>0.09 micrograms per liter [µg/L]) in water systems serving Alabama, Colorado, Georgia, the

Northern Mariana Islands, and Pennsylvania [ADDIN EN.CITE ADDIN EN.CITE.DATA]. These utilities used both ground and surface drinking water sources, with PFBS concentrations ranging from 0.09 to 0.37 µg/L. The estimated combined number of people served by these water systems is more than 340,000 [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2018</Year><RecNum>1243</RecNum><IDText>4339794</IDText><DisplayText>(U.S. EPA, 2018)</DisplayText><record><rec-number>1243</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1243</key></foreign-keys><ref-type name="Computer Program">9</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Safe drinking water information system</title></titles><dates><year>2018</year></dates><label>4339794</label><work-type>Database</work-type><urls><related-urls><url>https://www3.epa.gov/enviro/facts/sdwis/search.html</url></related-urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>].

Measurements from 37 surface water bodies in the northeastern United States (metropolitan New York area and Rhode Island) collected in 2014 showed an 85% site detection rate [ADDIN EN.CITE <EndNote><Cite><Author>Zhang</Author><Year>2016</Year><RecNum>1184</RecNum><IDText>3470830</IDText><DisplayText>(Zhang et al., 2016)</DisplayText><record><rec-number>1184</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1184</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zhang, X.</author><author>Lohmann, R.</author><author>Dassuncao, C.</author><author>Hu, X. C.</author><author>Weber, A. K.</author><author>Vecitis, C. D.</author><author>Sunderland, E. M.</author></authors></contributors><titles><title>Source attribution of poly- and perfluoroalkyl substances (PFASs) in surface waters from Rhode Island and the New York metropolitan area</title><secondary-title>Environmental Science & Technology Letters</secondary-title><alt-title>Environ Sci Technol Lett</alt-title><short-title>Environmental Science & Technology Letters</short-title></titles><periodical><full-title>Environmental Science & Technology Letters</full-title><abbr-1>Environ Sci Technol Lett</abbr-1></periodical><alt-periodical><full-title>Environmental Science & Technology Letters</full-title><abbr-1>Environ Sci Technol Lett</abbr-1></alt-periodical><pages>316-321</pages><volume>3</volume><number>9</number><dates><year>2016</year></dates><isbn>EISSN 2328-8930</isbn><accession-num>28217711</accession-num><label>3470830</label><urls><related-urls><url>http://dx.doi.org/10.1021/acs.estlett.6b00255</url></related-urls></urls><electronic-resource-num>10.1021/acs.estlett.6b00255</electronic-resource-num><language>English</language></record></Cite></EndNote>]. PFBS has also been identified in surface waters in Georgia, New Jersey, North Carolina, and the Upper Mississippi River Basin [ADDIN EN.CITE ADDIN EN.CITE.DATA]. It has also been detected in

wastewater treatment plant effluent, seawater, soil, and biosolids [ADDIN EN.CITE ADDIN EN.CITE.DATA].

PFBS contamination, which has been associated with the use of aqueous film-forming foams (AFFFs) [ADDIN EN.CITE ADDIN EN.CITE.DATA], was reported at Superfund sites and areas under assessment for Superfund designation. Contaminated sites include the former Wurtsmith Air Force Base, Ellsworth Air Force Base, and Dover Air Force Base [ADDIN EN.CITE ADDIN EN.CITE.DATA]. At the Wurtsmith site, PFBS was detected at a concentration of 6.4 µg/L in groundwater contaminated by a PFAS plume originating from the fire training area [ADDIN EN.CITE <EndNote><Cite><Author>ASTSWMO</Author><Year>2015</Year><RecNum>1245</RecNum><IDText>4339280</IDText><DisplayText>(ASTSWMO, 2015)</DisplayText><record><rec-number>1245</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1245</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ASTSWMO,</author></authors></contributors><titles><title>Perfluorinated chemicals (PFCS): Perfluorooctanoic acid (PFOA) & perfluorooctane sulfonate (PFOS) information paper</title></titles><dates><year>2015</year></dates><label>4339280</label><urls></urls><language>English</language><modified-date>Association of State and Territorial Solid Waste Management Officials</modified-date></record></Cite></EndNote>]. It is also present in some drinking water samples from nearby residential wells at low nanograms per liter concentrations, which were below the screening value cited by the Michigan Department of Community Health [ADDIN EN.CITE <EndNote><Cite><Author>MDCH</Author><Year>2015</Year><RecNum>1237</RecNum><IDText>4613765</IDText><DisplayText>(MDCH, 2015)</DisplayText><record><rec-number>1237</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1237</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>MDCH,</author></authors></contributors><titles><title>Letter health consultation: Evaluation of drinking water near Wurtsmith Air Force Base, Oscoda, Iosco County, Michigan</title></titles><dates><year>2015</year></dates><pub-location>Atlanta, GA</pub-location><publisher>U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease</publisher><label>4613765</label><work-type>Personal Communication</work-type><urls><related-urls><url>https://www.atsdr.cdc.gov/HAC/pha/WurtsmithAFB/WurtsmithAFB_H2O_%20LHC_09-08-2015_508.pdf</url></related-urls></urls><language>English</language><modified-date>Michigan Department of Community Health</modified-date></record></Cite></EndNote>]. Other sources of PFAS and/or PFBS contamination include chrome plating operations, PFAS manufacture, and sites that use PFAS in product formulations such as textile and electronics facilities.

PFBS has also been detected in household dust and consumer products. There was a 92% detection frequency for PFBS among 39 household dust samples (10 from the United States) analyzed with levels ranging from 86 nanograms per gram (ng/g) for the 25th percentile to

782 ng/g for the 75th percentile [ADDIN EN.CITE
<EndNote><Cite><Author>Kato</Author><Year>2009</Year><RecNum>879</RecNum><ID
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523</pages><volume>109</volume><number>5</number><dates><year>2009</year></dates>
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urls></urls><electronic-resource-num>10.1016/j.envres.2009.01.005</electronic-resource-
num><language>English</language></record></Cite></EndNote>]. In a separate study, PFBS dust levels were measured in Boston area offices (n = 31), homes (n = 30), and vehicles (n = 13) with detection frequencies being relatively low—10, 3, and 0%, respectively—and ranging in the low parts per billion [ADDIN EN.CITE
<EndNote><Cite><Author>Fraser</Author><Year>2013</Year><RecNum>958</RecNum><I
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A. J.</author><author>Webster, T. F.</author><author>Watkins, D.
J.</author><author>Strynar, M. J.</author><author>Kato, K.</author><author>Calafat, A.
M.</author><author>Vieira, V. M.</author><author>McClean, M.
D.</author></authors></contributors><titles><title>Polyfluorinated compounds in dust from
homes, offices, and vehicles as predictors of concentrations in office workers'
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urls></urls><electronic-resource-num>10.1016/j.envint.2013.08.012</electronic-resource-
num><language>English</language></record></Cite></EndNote>]. Consumer products could also be an exposure source. Limited quantitative testing showed the presence of PFBS in carpet and upholstery protectors (45.8 and 89.6 ng/g), carpet shampoo (25.7 and 911 ng/g), textiles

(2 ng/g), and floor wax (143 ng/g) purchased in the United States [ADDIN EN.CITE <EndNote><Cite><Author>Liu</Author><Year>2014</Year><RecNum>792</RecNum><IDText>2324799</IDText><DisplayText>(Liu et al., 2014)</DisplayText><record><rec-number>792</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">792</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Liu, X.</author><author>Guo, Z.</author><author>Krebs, K. A.</author><author>Pope, R. H.</author><author>Roache, N. F.</author></authors></contributors><titles><title>Concentrations and trends of perfluorinated chemicals in potential indoor sources from 2007 through 2011 in the US</title><secondary-title>Chemosphere</secondary-title><alt-title>Chemosphere</alt-title><short-title>Chemosphere</short-title></titles><periodical><full-title>Chemosphere</full-title><abbr-1>Chemosphere</abbr-1></periodical><alt-periodical><full-title>Chemosphere</full-title><abbr-1>Chemosphere</abbr-1></alt-periodical><pages>51-57</pages><volume>98</volume><dates><year>2014</year></dates><isbn>ISSN 0045-6535
EISSN 1879-1298</isbn><accession-num>24268172</accession-num><label>2324799</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.chemosphere.2013.10.001</url></related-urls></urls><electronic-resource-num>10.1016/j.chemosphere.2013.10.001</electronic-resource-num><language>English</language></record></Cite></EndNote>].

PFBS was detected in fast food packaging (7/20 samples) in one U.S. study [ADDIN EN.CITE <EndNote><Cite><Author>Schaider</Author><Year>2017</Year><RecNum>1182</RecNum><IDText>3981864</IDText><DisplayText>(Schaider et al., 2017)</DisplayText><record><rec-number>1182</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1182</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Schaider, L. A.</author><author>Balan, S. A.</author><author>Blum, A.</author><author>Andrews, D. Q.</author><author>Strynar, M. J.</author><author>Dickinson, M. E.</author><author>Lunderberg, D. M.</author><author>Lang, J. R.</author><author>Peaslee, G. F.</author></authors></contributors><titles><title>Fluorinated compounds in US fast food packaging</title><secondary-title>Environmental Science & Technology Letters</secondary-title><alt-title>Environ Sci Technol Lett</alt-title><short-title>Environmental Science & Technology Letters</short-title></titles><periodical><full-title>Environmental Science & Technology Letters</full-title><abbr-1>Environ Sci Technol Lett</abbr-1></periodical><alt-periodical><full-title>Environmental Science & Technology Letters</full-title><abbr-1>Environ Sci Technol Lett</abbr-1></alt-periodical><pages>105-111</pages><volume>4</volume><number>3</number><dates><year>2017</year></dates><isbn>EISSN 2328-8930</isbn><accession-num>30148183</accession-num><label>3981864</label><urls><related-urls><url>http://dx.doi.org/10.1021/acs.estlett.6b00435</url></related-urls></urls><electronic-resource-num>10.1021/acs.estlett.6b00435</electronic-resource-

num><language>English</language></record></Cite></EndNote>] although the magnitude of the detection was not reported.

The European Food Safety Authority reported the presence of PFBS in various food and drink items, including fruits, vegetables, cheese, and bottled water. For average adult consumers, the estimated exposure ranges for PFBS were 0.03−1.89 nanograms per kilogram per day (ng/kg-day) (minimum) to 0.10−3.72 ng/kg-day (maximum) [ADDIN EN.CITE <EndNote><Cite><Author>EFSA</Author><Year>2012</Year><RecNum>1060</RecNum><IDText>4339387</IDText><DisplayText>(EFSA, 2012)</DisplayText><record><rec-number>1060</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1060</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EFSA,</author></authors></contributors><titles><title>Perfluoroalkylated substances in food: Occurrence and dietary exposure</title><secondary-title>European Food Safety Authority Journal</secondary-title><alt-title>EFSA J</alt-title><short-title>European Food Safety Authority Journal</short-title></titles><periodical><full-title>European Food Safety Authority Journal</full-title><abbr-1>EFSA J</abbr-1></periodical><alt-periodical><full-title>European Food Safety Authority Journal</full-title><abbr-1>EFSA J</abbr-1></alt-periodical><pages>2743</pages><volume>10</volume><number>6</number><dates><year>2012</year></dates><isbn>ISSN 1830-5458</isbn><label>4339387</label><urls></urls><language>English</language><modified-date>European Food Safety Authority</modified-date></record></Cite></EndNote>].

PFBS has been reported in serum of humans in the general population. In American Red Cross samples collected in 2015, 8.4% had a quantifiable serum PFBS concentration; the majority of samples were below the lower limit of quantitation (4.2 nanograms per milliliter [ng/mL]) [ADDIN EN.CITE <EndNote><Cite><Author>Olsen</Author><Year>2017</Year><RecNum>875</RecNum><IDText>3856451</IDText><DisplayText>(Olsen et al., 2017)</DisplayText><record><rec-number>875</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">875</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Olsen, G. W.</author><author>Mair, D. C.</author><author>Lange, C. C.</author><author>Harrington, L. M.</author><author>Church, T. R.</author><author>Goldberg, C. L.</author><author>Herron, R. M.</author><author>Hanna, H.</author><author>Nobiletti, J. B.</author><author>Rios, J. A.</author><author>Reagen, W. K.</author><author>Ley, C. A.</author></authors></contributors><titles><title>Per- and polyfluoroalkyl substances (PFAS) in American Red Cross adult blood donors, 2000-2015</title><secondary-title>Environmental Research</secondary-title><alt-title>Environ Res</alt-title><short-title>Environmental Research</short-title></titles><periodical><full-title>Environmental Research</full-title><abbr-1>Environ Res</abbr-1></periodical><alt-periodical><full-title>Environmental Research</full-title><abbr-1>Environ Res</abbr-1></alt-periodical><pages>87-95</pages><volume>157</volume><number>Elsevier</number><dates><year>2017</year></

dates><isbn>ISSN 0013-9351
EISSN 1096-0953</isbn><accession-num>28528142</accession-num><label>3856451</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.envres.2017.05.013</url></related-urls></urls><electronic-resource-num>10.1016/j.envres.2017.05.013</electronic-resource-num><language>English</language></record></Cite></EndNote>]. The National Health and Nutrition Examination Survey (NHANES) included PFBS in consecutive biomonitoring cycles, including 2013–2014 where the 95th percentile reported for PFBS was at or below the level of detection (0.1 ng/mL). Considering the relatively rapid rate of elimination of PFBS (days to weeks), compared with longer chain PFAS (years), the lack of biomonitoring detects (e.g., NHANES 2013–2014 cycle) should not be interpreted as a lack of occurrence or exposure potential. Another study with a lower limit of detection (0.013 ng/g) reported increasing levels of PFBS in serum from primiparous nursing women in Sweden from 1996 to 2010 [ADDIN EN.CITE <EndNote><Cite><Author>Glynn</Author><Year>2012</Year><RecNum>924</RecNum><IDText>1578498</IDText><DisplayText>(Glynn et al., 2012)</DisplayText><record><rec-number>924</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">924</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Glynn, A.</author><author>Berger, U.</author><author>Bignert, A.</author><author>Ullah, S.</author><author>Aune, M.</author><author>Lignell, S.</author><author>Darnerud, P. O.</author></authors></contributors><titles><title>Perfluorinated alkyl acids in blood serum from primiparous women in Sweden: serial sampling during pregnancy and nursing, and temporal trends 1996-2010</title><secondary-title>Environmental Science and Technology</secondary-title><alt-title>Environ Sci Technol</alt-title><short-title>Environmental Science and Technology</short-title></titles><periodical><full-title>Environmental Science and Technology</full-title><abbr-1>Environ Sci Technol</abbr-1></periodical><alt-periodical><full-title>Environmental Science and Technology</full-title><abbr-1>Environ Sci Technol</abbr-1></alt-periodical><pages>9071-9079</pages><volume>46</volume><number>16</number><dates><year>2012</year></dates><isbn>ISSN 0013-936X
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1.3 TOXICOKINETICS

1.3.1 Overview

Animal evidence has shown that PFBS, like other PFAS, is well absorbed following oral administration. PFBS distributes to all tissues of the body [ADDIN EN.CITE <EndNote><Cite><Author>Bogdanska</Author><Year>2014</Year><RecNum>794</RecNum><IDText>2324789</IDText><DisplayText>(Bogdanska et al., 2014)</DisplayText><record><rec-number>794</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">794</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bogdanska,

J.</author><author>Sundstrom, M.</author><author>Bergstrom, U.</author><author>Borg, D.</author><author>Abedi-Valugerdi, M.</author><author>Bergman, A.</author><author>Depierre, J.</author><author>Nobel, S.</author></authors></contributors><titles><title>Tissue distribution of S-35-labelled perfluorobutanesulfonic acid in adult mice following dietary exposure for 1-5 days</title><secondary-title>Chemosphere</secondary-title><alt-title>Chemosphere</alt-title><short-title>Chemosphere</short-title></titles><periodical><full-title>Chemosphere</full-title><abbr-1>Chemosphere</abbr-1></periodical><alt-periodical><full-title>Chemosphere</full-title><abbr-1>Chemosphere</abbr-1></alt-periodical><pages>28-36</pages><volume>98</volume><dates><year>2014</year></dates><isbn>ISSN 0045-6535
EISSN 1879-1298</isbn><accession-num>24238775</accession-num><label>2324789</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.chemosphere.2013.09.062</url></related-urls></urls><electronic-resource-num>10.1016/j.chemosphere.2013.09.062</electronic-resource-num><language>English</language></record></Cite></EndNote>], but a study evaluating the volume of distribution (V_d) concluded that distribution is predominantly extracellular [ADDIN EN.CITE <EndNote><Cite><Author>Olsen</Author><Year>2009</Year><RecNum>1045</RecNum><IDText>1326734</IDText><DisplayText>(Olsen et al., 2009)</DisplayText><record><rec-number>1045</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1045</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Olsen, G. W.</author><author>Chang, S. C.</author><author>Noker, P. E.</author><author>Gorman, G. S.</author><author>Ehresman, D. J.</author><author>Lieder, P. H.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>A comparison of the pharmacokinetics of perfluorobutanesulfonate (PFBS) in rats, monkeys, and humans</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>65-74</pages><volume>256</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>19059455</accession-num><label>1326734</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2008.11.008</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2008.11.008</electronic-resource-num><language>English</language></record></Cite></EndNote>]. Because of its resistance to metabolic degradation, PFBS is primarily eliminated unchanged in urine and feces.

Three sets of investigators have conducted toxicokinetic studies in rats and monkeys [ADDIN EN.CITE ADDIN EN.CITE.DATA]. [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"] and [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6781357"] have measured the half-life of PFBS in humans. [HYPERLINK

"https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=2324789"] and [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6579272"] have reported limited toxicokinetic information in mice. One study developed a physiologically based pharmacokinetic (PBPK) model that includes parameterization for PFBS [ADDIN EN.CITE <EndNote><Cite><Author>Fàbrega</Author><Year>2015</Year><RecNum>1026</RecNum><IDText>3223669</IDText><DisplayText>(Fàbrega et al., 2015)</DisplayText><record><rec-number>1026</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1026</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Fàbrega, F.</author><author>Kumar, V.</author><author>Benfenati, E.</author><author>Schuhmacher, M.</author><author>Domingo, J. L.</author><author>Nadal, M.</author></authors></contributors><titles><title>Physiologically based pharmacokinetic modeling of perfluoroalkyl substances in the human body</title><secondary-title>Toxicological and Environmental Chemistry</secondary-title><alt-title>Toxicol Environ Chem</alt-title><short-title>Toxicological and Environmental Chemistry</short-title></titles><periodical><full-title>Toxicological and Environmental Chemistry</full-title><abbr-1>Toxicol Environ Chem</abbr-1></periodical><alt-periodical><full-title>Toxicological and Environmental Chemistry</full-title><abbr-1>Toxicol Environ Chem</abbr-1></alt-periodical><pages>814-827</pages><volume>97</volume><number>6</number><dates><year>2015</year></dates><isbn>ISSN 0277-2248
EISSN 1029-0486</isbn><label>3223669</label><urls><related-urls><url>http://dx.doi.org/10.1080/02772248.2015.1060976</url></related-urls></urls><electronic-resource-num>10.1080/02772248.2015.1060976</electronic-resource-num><language>English</language></record></Cite></EndNote>].

Results of all studies discussed in this section are summarized in Table 2.

Table [SEQ Table * ARABIC]. Summary of the Toxicokinetics of Serum PFBS (Mean ± SE)						
Species/Sex	**Study Design**	**Elimination Half-Life (hr)**	**AUC (µg-hr/mL)**	**Clearance**	**V_d (L/kg)**	**Reference**
Mice						
Mice/male	Single oral dose (30 mg/kg)	3.7	1,515	0.019 (L/hr-kg)	0.129	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6579272"]
	Single oral dose (300 mg/kg)	6.0	7,178	0.039 (L/hr-kg)	0.291	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6579272"]
	Single oral dose (combined 30/300 mg/kg)	5.8		0.038 (L/hr-kg)	0.275	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6579272"]
Mice/female	Single oral dose (30 mg/kg)	4.4	520	0.056 (L/hr-kg)	0.145	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6579272"]
	Single oral dose (300 mg/kg)	4.6	4,587	0.064 (L/hr-kg)	0.308	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6579272"]
	Single oral dose (combined 30/300 mg/kg)	4.5		0.063 (L/hr-kg)	0.278	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6579272"]

Table [SEQ Table * ARABIC]. Summary of the Toxicokinetics of Serum PFBS (Mean ± SE)

Species/Sex	Study Design	Elimination Half-Life (hr)	AUC (µg-hr/mL)	Clearance	V_d (L/kg)	Reference
Rats						
Rats/male	Single i.v. dose (10 mg/kg)	2.1	254	0.0394 (L/hr-kg)	0.118	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=2850396"]
	Single i.v. dose (30 mg/kg)	4.51 ± 2.22[a]	294 ± 77	119 ± 34 (mL/hr)[b]	0.330 ± 0.032	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"]
	Single oral dose (30 mg/kg)	4.68 ± 0.43[a]	163 ± 10	NA	0.676 ± 0.055	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"]
	Single i.v. dose (4 mg/kg)	4.22 ± 0.28[c]	116 ± 7	0.0345 ± 0.002 (L/hr-kg)	0.188 ± 0.017[c]	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5387170"]
	Single oral dose (4 mg/kg)	4.89 ± 1.67[c]	154 ± 15	0.0265 ± 0.003 (L/hr-kg)	0.174 ± 0.614[c]	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5387170"]
	Single oral dose (20 mg/kg)	5.36 ± 1.24[c]	533 ± 45	0.0376 ± 0.003 (L/hr-kg)	0.167 ± 0.039[c]	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5387170"]

Table [SEQ Table * ARABIC]. Summary of the Toxicokinetics of Serum PFBS (Mean ± SE)

Species/Sex	Study Design	Elimination Half-Life (hr)	AUC (µg-hr/mL)	Clearance	V_d (L/kg)	Reference
	Single oral dose (100 mg/kg)	5.25 ± 1.19[c]	1,320 ± 100	0.0755 ± 0.006 (L/hr-kg)	0.335 ± 0.041[c]	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5387170"]
Rats/female	Single i.v. dose (10 mg/kg)	0.64	32	0.311 (L/hr-kg)	0.288	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=2850396"]
	Single i.v. dose (30 mg/kg)	3.96 ± 0.21[a]	65 ± 5	469 ± 40 (mL/hr)[d]	0.351 ± 0.034	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"]
	Single oral dose (30 mg/kg)	7.42 ± 0.79[a]	85 ± 12	NA	0.391 ± 0.105	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"]
	Single i.v. dose (4 mg/kg)	0.95 ± 0.10[c]	16 ± 1	0.252 ± 0.018 (L/hr-kg)	0.165 ± 0.015[c]	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5387170"]
	Single oral dose (4 mg/kg)	1.50 ± 0.10[c]	29 ± 3	0.152 ± 0.020 (L/hr-kg)	0.328 ± 0.042[c]	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5387170"]

Table [SEQ Table * ARABIC]. Summary of the Toxicokinetics of Serum PFBS (Mean ± SE)						
Species/Sex	**Study Design**	**Elimination Half-Life (hr)**	**AUC (µg-hr/mL)**	**Clearance**	**V_d (L/kg)**	**Reference**
	Single oral dose (20 mg/kg)	1.23 ± 0.12[c]	109 ± 23	0.183 ± 0.039 (L/hr-kg)	0.326 ± 0.073[c]	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5387170"]
	Single oral dose (100 mg/kg)	1.11 ± 0.10[c]	387 ± 50	0.259 ± 0.033 (L/hr-kg)	0.415 ± 0.063[c]	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5387170"]
Monkeys[b]						
Cynomolgus macaque/male	Single i.v. dose (10 mg/kg)	15 (9.65)[e]	1,115 ± 859	0.016 (L/hr-kg)	0.209 ± 0.028	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=2850396"]
	Single i.v. dose (10 mg/kg)	95.2 ± 27.1	24.3 ± 8.6	511 ± 141 (mL/hr)	0.254 ± 0.031	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"]
Cynomolgus macaque/female	Single i.v. dose (10 mg/kg)	8.1	489 ± 180	0.0229 ± 0.0099 (L/hr-kg)	0.248 ± 0.045	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=2850396"]
	Single i.v. dose (10 mg/kg)	83.2 ± 41.9	35.4 ± 13.3	368 ± 120 (mL/hr)	0.255 ± 0.017	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"]

Table [SEQ Table * ARABIC]. Summary of the Toxicokinetics of Serum PFBS (Mean ± SE)						
Species/Sex	**Study Design**	**Elimination Half-Life (hr)**	**AUC (µg-hr/mL)**	**Clearance**	**V_d (L/kg)**	**Reference**
Humans						
Males and female	Occupational (*n* = 6)	619.2[f]	NA	NA	NA	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"]
Males	Occupational (*n* =5)	552[f]	NA	NA	NA	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"]
Female	Occupational (*n* = 1)	1,096.8	NA	NA	NA	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"]
Males and females	Occupational (*n* = 26)	1,056	NA	NA	NA	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6781357"]

Table [SEQ Table * ARABIC]. Summary of the Toxicokinetics of Serum PFBS (Mean ± SE)

Species/Sex	Study Design	Elimination Half-Life (hr)	AUC (µg-hr/mL)	Clearance	V_d (L/kg)	Reference

[a][HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"]_reported $t_{1/2,\alpha}$ and $t_{1/2,\beta}$ in rats, presenting data for $t_{1/2,\beta}$.
[b]Body weights were reported to be 0.200−0.250 kg (with corresponding clearance of approximately 476 mL/hr-kg).
[c][HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5387170"] reported $t_{1/2,\alpha}$, $t_{1/2,\beta}$, and $t_{1/2}k_{10}$ in male rats (both oral and i.v.) and female rats (i.v. only); only $t_{1/2}k_{10}$ was reported in female rats (oral). Presenting data for $t_{1/2,\beta}$ for male rats (both oral and i.v.) and female rats (i.v.) and $t_{1/2}k_{10}$ for female rats (oral). The volume of distribution (V_d) was calculated as the sum of volume terms of the central compartment and that of the peripheral compartment except for orally exposed female rats. The volume of the peripheral compartment was not reported for orally exposed female rats, representing the volume of the central compartment only.
[d]The data were monitored 48 hours and 31 days postdosing for [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=2850396"] and [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"], respectively.
[e]One male monkey had a serum concentration more than 10-fold higher than the others at 48 hours postdosing with an estimated PFBS half-life of 26 hours.
[f][HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"] reported mean and geometric mean values for males only and all subjects, presenting data for geometric mean values.

AUC = area under the curve; i.v. = intravenous; NA = not available; PFBS = perfluorobutane sulfonic acid; SE = standard error; $t_{1/2}$ = half-life; V_d = volume of distribution.

1.3.2 Absorption

[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"] conducted intravenous (i.v.) and oral uptake studies in rats (n = 3/sex) that were given a single dose (30 milligrams per kilogram [mg/kg]) of potassium PFBS (K^+PFBS). The serum area under the concentration curve (AUC) after i.v. administration was 294 ± 77 and 65 ± 5 (µg-hour/mL) in male and female rats, respectively, and 163 ± 10 and 85 ± 12 in males and females, respectively, after oral dosing. The large variance in AUC for male rats after i.v. dosing and greater AUC after oral dosing compared to i.v. dosing in females makes it difficult to interpret these results with certainty, but it seems that PFBS is 100% bioavailable in female rats, whereas the nominal bioavailability in male rats is only 55% based on AUC. Peak concentrations (C_{max}) occurred at 0.3−0.4 hours after oral dosing, showing that absorption was fairly rapid. Bioavailability based on C_{max} was 60% in male rats and 85% in female rats, suggesting a similar sex difference as estimated from the AUCs.

The above findings are generally confirmed by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5387170"] who found that absorption of PFBS usually occurred within 24 hours, along with the time reaching the maximal plasma concentration (T_{max}) under 2.4 hours in male rats and under 1.4 hours in female rats, following a single dose of gavage administration in Hsd:Sprague-Dawley (S-D) rats (4, 20, 100 mg/kg of K^+PFBS). However, bioavailability calculated based on the AUC after i.v. and oral doses of 4 mg/kg reported by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5387170"] was 75% in males and 60% in females. The C_{max} values of 45% and 27% in males and females, respectively, are qualitatively the opposite of the results from [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"].

Given the range of estimated bioavailability from the results of [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"] and [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5387170"], a difference in this parameter between male and female rats cannot be determined. Averaging the AUC-based values for both males and females from the two studies yields an overall average of 73%.

Notably, [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5387170"] also observed that the dose-adjusted AUC decreased with increasing doses for both males and females. However, this result could be attributed to saturation of renal resorption at higher doses, rather than a reduction in absorption.

Similar observations indicating rapid absorption of PFBS have been reported for CD-1 mice orally exposed to PFBS at 30 or 300 mg/kg, where T_{max} was estimated to occur between 1 and 2 hours after gavage [ADDIN EN.CITE <EndNote><Cite><Author>Lau</Author><Year>2020</Year><RecNum>1040</RecNum><IDText>6579272</IDText><DisplayText>(Lau et al., 2020)</DisplayText><record><rec-number>1040</rec-number><foreign-keys><key app="EN" db-

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EISSN 1879-3185</isbn><accession-num>32534104</accession-num><label>6579272</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2020.152522</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2020.152522</electronic-resource-num><language>English</language></record></Cite></EndNote>].

1.3.3 Distribution

PFBS has been shown to distribute to tissues within 24 hours of exposure, with the liver and kidney being the organs with highest distribution. [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6579272"] evaluated the pharmacokinetic properties of PFBS in CD-1 mice at 8 weeks of age. Male and female mice were given a single dose of 0, 30, or 300 mg/kg body weight PFBS via gavage. The liver and kidneys were harvested 24 hours postdosing. PFBS distributed to both organs readily in a dose-dependent manner but did not accumulate in either organ. [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6579272"] reported similar combined V_d values of 0.275 or 0.278 liter per kilogram [L/kg] in male and female mice, respectively (Table 2).

[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"] estimated volumes of distribution for K^+PFBS as 0.7 and 0.4 L/kg in male and female rats, respectively, and 0.25 L/kg in male and female cynomolgus macaques and concluded that K^+PFBS is primarily distributed in the extracellular space. Consistent with the observations by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"], [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5387170"] found that the overall V_d for PFBS was generally comparable between male rats (0.167–0.335 L/kg) and female rats (0.165–0.415 L/kg). [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=2850396"] calculated a V_d of 0.248 L/kg in female cynomolgus macaques, consistent with females from [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"]. The male monkey V_d from [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=2850396"] was slightly

lower (0.209 L/kg) than corresponding females and males from [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"]. These results indicate V_d is generally comparable between male and female monkeys. [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5387170"] also evaluated tissue concentrations in the liver, kidney, and brain of male and female rats and reported higher PFBS concentrations in the liver than the kidney, with the lowest concentrations occurring in the brain.

[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=2324789"] characterized the tissue distribution of ^{35}S-labeled PFBS in male C57BL/6 mice. The animals (3/group) were exposed for either 1, 3, or 5 days to an average of 16 mg of PFBS/kg-day in the diet. Following 1, 3, and 5 days of exposure, the total estimated recovery of PFBS from all tissues evaluated was 10, 5, and 3.4% of the ingested dose, respectively. The declining recovery with time reflects the lack of accumulation in tissues after the first few days, with continued elimination in the urine. The study authors suggested that these low recovery rates most likely reflect rapid excretion of PFBS and/or potentially limited uptake of the compound; however, the results of [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6579272"] and [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"] suggest that limited tissue distribution is also a factor.

[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=2324789"] found that blood levels of PFBS did not change when comparing values observed after 1 and 5 days of exposure. As with PFOS, PFBS was found to distribute to most of the 20 tissues examined at all exposure durations, but the levels of PFBS were significantly lower (fivefold to 40-fold lower) than those of PFOS in tissues after similar exposure to PFOS, especially in liver and lungs [ADDIN EN.CITE <EndNote><Cite><Author>Bogdanska</Author><Year>2014</Year><RecNum>794</RecNum><IDText>2324789</IDText><DisplayText>(Bogdanska et al., 2014)</DisplayText><record><rec-number>794</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">794</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bogdanska, J.</author><author>Sundstrom, M.</author><author>Bergstrom, U.</author><author>Borg, D.</author><author>Abedi-Valugerdi, M.</author><author>Bergman, A.</author><author>Depierre, J.</author><author>Nobel, S.</author></authors></contributors><titles><title>Tissue distribution of S-35-labelled perfluorobutanesulfonic acid in adult mice following dietary exposure for 1-5 days</title><secondary-title>Chemosphere</secondary-title><alt-title>Chemosphere</alt-title><short-title>Chemosphere</short-title></titles><periodical><full-title>Chemosphere</full-title><abbr-1>Chemosphere</abbr-1></periodical><alt-periodical><full-title>Chemosphere</full-title><abbr-1>Chemosphere</abbr-1></alt-periodical><pages>28-36</pages><volume>98</volume><dates><year>2014</year></dates><isbn>ISSN 0045-

6535
EISSN 1879-1298</isbn><accession-num>24238775</accession-num><label>2324789</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.chemosphere.2013.09.062</url></related-urls></urls><electronic-resource-num>10.1016/j.chemosphere.2013.09.062</electronic-resource-num><language>English</language></record></Cite></EndNote>]. These differences might be attributed to chain-length-dependent active transport of perfluorinated chemicals [ADDIN EN.CITE <EndNote><Cite><Author>Weaver</Author><Year>2010</Year><RecNum>1034</RecNum><DisplayText>(Weaver et al., 2010)</DisplayText><record><rec-number>1034</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1034</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Weaver, Y. M.</author><author>Ehresman, D. J.</author><author>Butenhoff, J. L.</author><author>Hagenbuch, B.</author></authors></contributors><titles><title>Roles of rat renal organic anion transporters in transporting perfluorinated carboxylates with different chain lengths</title><secondary-title>Toxicological Sciences</secondary-title><alt-title>Toxicol Sci</alt-title><short-title>Toxicological Sciences</short-title></titles><periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></periodical><alt-periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></alt-periodical><pages>305-314</pages><volume>113</volume><number>2</number><dates><year>2010</year></dates><isbn>ISSN 1096-6080
EISSN 1096-0929</isbn><accession-num>19915082</accession-num><label>2010072</label><urls><related-urls><url>http://dx.doi.org/10.1093/toxsci/kfp275</url></related-urls></urls><electronic-resource-num>10.1093/toxsci/kfp275</electronic-resource-num><language>English</language></record></Cite></EndNote>]. Excluding stomach and fat tissue, PFBS tissue levels increased between 1 and 3 days of exposure, but there were no significant changes in tissue levels between 3 and 5 days of exposure in any tissue examined. As with PFOS, whole bone, liver, blood, skin, and muscle accounted for approximately 90% of the recovered PFBS at all time points. The highest tissue concentrations outside of blood, however, were found in the liver, GI tissues, kidney, and cartilage. The significant total PFBS mass found in muscle and skin was due to the large total volume of these tissues rather than the per unit concentration in them. The liver contained the highest tissue concentration of PFBS at all time points, while the brain contained the lowest.

Human studies were not available on lactational transfer of PFBS. Studies are sparse pertaining to the transplacental transfer of PFBS in humans; in a Spanish mother-child paired cohort, PFBS was not found in maternal blood samples or in corresponding cord blood during the first trimester of pregnancy [ADDIN EN.CITE <EndNote><Cite><Author>Manzano-Salgado</Author><Year>2015</Year><RecNum>876</RecNum><IDText>3448674</IDText><DisplayText>(Manzano-Salgado et al., 2015)</DisplayText><record><rec-number>876</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">876</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Manzano-Salgado, C. B.</author><author>Casas, M.</author><author>Lopez-Espinosa, M. J.</author><author>Ballester, F.</author><author>Basterrechea, M.</author><author>Grimalt,

J. O.</author><author>Jiménez, A. M.</author><author>Kraus, T.</author><author>Schettgen, T.</author><author>Sunyer, J.</author><author>Vrijheid, M.</author></authors></contributors><titles><title>Transfer of perfluoroalkyl substances from mother to fetus in a Spanish birth cohort</title><secondary-title>Environmental Research</secondary-title><alt-title>Environ Res</alt-title><short-title>Environmental Research</short-title></titles><periodical><full-title>Environmental Research</full-title><abbr-1>Environ Res</abbr-1></periodical><alt-periodical><full-title>Environmental Research</full-title><abbr-1>Environ Res</abbr-1></alt-periodical><pages>471-478</pages><volume>142</volume><dates><year>2015</year></dates><isbn>ISSN 0013-9351
EISSN 1096-0953</isbn><accession-num>26257032</accession-num><label>3448674</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.envres.2015.07.020</url></related-urls></urls><electronic-resource-num>10.1016/j.envres.2015.07.020</electronic-resource-num><language>English</language></record></Cite></EndNote>]. However, developmental studies in animals indicate the potential for effects in offspring following gestational exposure, suggesting direct (i.e., fetus) and/or indirect (maternal/pregnant dam) effects of PFBS on offspring [ADDIN EN.CITE ADDIN EN.CITE.DATA].

Volume of distribution is expected to be similar across mammalian species. For PFBS, the average value for male and female monkeys (0.23 L/kg) is in the range estimated for male and female rats by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5387170"] (0.17–0.42 L/kg), although estimates by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"] were slightly higher.

1.3.4 Metabolism

There is no evidence of biotransformation of PFBS. It is expected that PFBS, a short-chain (C4) of perfluoroalkyl acids (PFAAs), is metabolically inert because of the chemical stability that also exists in the longer chain PFAA chemicals, including perfluorohexane sulfonic acid (PFHxS) (C6), PFOS (C8), and perfluorooctanoic acid (PFOA) (C8).

1.3.5 Excretion

To facilitate comparison of differing studies for a given species, results for excretion are organized by species.

1.3.5.1 Mice

[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6579272"] dosed male and female CD-1 mice with 0, 30, or 300 mg/kg body weight PFBS via a single gavage dose. Trunk blood was collected at 0.5, 1, 2, 4, 8, 16, 24, and 48 hours after dosing and urine at 24 hours after dosing. Within 24 hours of dosing, more than 95% of the PFBS measured in serum was excreted into urine. Although the rate of PFBS clearance was linear with administered doses, urine accounted for only 30–43% of the original gavage doses. The half-life of PFBS was estimated to be 4.5 hours in the female mice and 5.8 hours in the males. Sex difference in PFBS elimination was also noted in that the elimination rate of absorbed PFBS was about 28% faster in female mice than male mice. Similarly, AUC estimates for the serum,

kidney, and liver compartments were higher in males than in females. The findings are generally comparable to previous studies on rats [ADDIN EN.CITE ADDIN EN.CITE.DATA].

1.3.5.2 Rats

[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=2850396"] conducted a single-dose pharmacokinetic study in S-D rats, designed to compare the toxicokinetic behavior of PFBS with that of perfluorohexanoic acid (PFHxA), another PFAA. In this study, 12 male and 12 female rats were each administered a bolus dose of PFBS (10 mg/kg) via i.v. injection. Blood samples were collected from three animals per sex at 0.5, 1, 1.5, 2, 4, 8, and 24 hours after dosing. Additionally, to determine urinary excretion, three animals per sex were housed in metabolic cages following dose administration and their urine collected over the following time intervals: 0–6, 6–12, and 12–24 hours postdosing. [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=2850396"] fit the data to a noncompartmental model to calculate pharmacokinetic parameters. Female rats had an approximately threefold shorter mean elimination half-life of PFBS in serum (0.64 hour) than male rats (2.1 hour). This result could be in part due to the difference in clearance and V_d. The mean apparent clearance of PFBS from the serum was approximately eightfold higher for female rats (0.311 L/hour-kg) than for male rats (0.0394 L/hour-kg), and the mean apparent V_d for PFBS in the serum was approximately 2.4-fold higher for female rats (0.288 L/kg) than for male rats (0.118 L/kg). Approximately 70% of the administered dose of PFBS was recovered in the urine over 24 hours postdosing regardless of sex. Using the urine data, the mean half-life values for male rats and female rats were determined to be 3.1 and 2.4 hours, respectively; the finding of longer urinary half-lives in males is consistent with those observed for serum half-lives.

[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"] evaluated the elimination of PFBS in S-D rats after i.v. and oral exposure to K^+PFBS. The terminal serum elimination half-lives following i.v. administration of 30 mg/kg K^+PFBS were 4.51 ± 2.22 hours for males and 3.96 ± 0.21 hours for females (mean ± standard deviation [SD]). Although there was no statistically significant difference between the terminal serum half-lives in male and female rats, there was a statistically significant difference in the urinary clearance rates ($p \leq 0.01$), with female rats (469 ± 40 mL/hour) having faster clearance rates than male rats (119 ± 34 mL/hour). Because clearance [CL] is calculated from the ratio of the volume of distribution [V_d] to the half-life [$t_{1/2}$], CL = 0.693 × V_d ÷ $t_{1/2}$, differences in V_d can lead to differences in CL, even when $t_{1/2}$ is similar between comparison groups. For rats receiving an oral dose, terminal serum K^+PFBS elimination half-lives were significantly different ($p \leq 0.05$) for males ($t_{1/2}$ = 4.68 ± 0.43 hour) versus females ($t_{1/2}$ = 7.42 ± 0.79 hour).

[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5387170"] also evaluated elimination of PFBS following a single i.v. or gavage dose in male or female Hsd:S-D rats (4, 20, 100 mg/kg of K^+PFBS). They reported elimination half-lives ($t_{1/2,\beta}$) following i.v. administration of PFBS in male and female rats of 4.22 and 0.95 hours, respectively. The data for male rats after both oral and i.v. dosing and female rats administered PFBS by i.v. fit a two-compartment model, whereas data in female rats dosed via gavage fit a one-compartment

model. Thus, elimination half-lives were only reported for male rats following oral exposure and ranged from 4.89−5.36 hours. Overall plasma elimination half-lives ($t_{1/2}$ k_{10}) reported in female rats after oral administration were between 1.11−1.50 hours, approximately three to fourfold faster than in males that ranged from 4.89−5.36 hours. Similarly, clearance was three to sixfold higher in females than males given the same dose (26.5−75.5 mL/hour-kg in males, 152−259 mL/hour-kg in females).

The serum K^+PFBS elimination half-lives reported by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5387170"] are consistent with the findings of [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"] in male rats but not in female rats. In general, the elimination half-life of serum PFBS observed by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5387170"] in female rats was two to fourfold shorter than seen by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"]. Similarly, [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=2850396"] calculated half-lives using a one compartment model for each group, whereas [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"] determined separate α and β phases via a two-compartment model. Thus, the half-life estimates of [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"] following i.v. administration (4.51−3.96 hours) are higher than those estimated by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=2850396"] based on urine data (0.64-2.1 hours).

1.3.5.3 Monkeys

Similar to their study in rats, [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=2850396"] investigated the toxicokinetic profile of PFBS through a series of experiments in the cynomolgus macaque (*Macaca fascicularis*). Monkeys (three males and three females) were each administered a bolus i.v. dose of 10 mg/kg PFBS. The controlled exposure to PFBS occurred 7 days after the same animals were each administered a bolus dose of PFHxA (10 mg/kg). Blood samples were collected at 0 hours (immediately prior to dosing) and at 1, 2, 4, 8, 24, and 48 hours after dose administration and were analyzed to determine PFBS concentration in serum. Only a single clearance half-life was estimated. The estimated half-life of PFBS in serum ranged from 5.8 to 26.0 hours in this experiment, and the median half-life was 9.55 hours for the six animals.

[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"] also evaluated the elimination of PFBS (specifically, K^+PFBS) in cynomolgus macaques after i.v. dosing. A significant difference in design from the study of [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=2850396"] is that [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"] followed

PFBS elimination for 31 days in monkeys (vs. 48 hours), allowing them to identify both an initial clearance half-life and a terminal-phase half-life. [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"] did not observe statistically significant sex-related differences in half-life or clearance between male and female monkeys, unlike those observed in rats. In monkeys, the mean terminal serum elimination half-lives, after i.v. administration of 10 mg/kg K^+PFBS, were 95.2 ± 27.1 hours in males and 83.2 ± 41.9 hours in females.

The serum half-life data in [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"] clearly show a slow elimination phase in monkeys that does not begin until 4–10 days after dosing. [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=2850396"] followed elimination for only 48 hours, hence could not have observed this terminal clearance phase. The initial elimination half-life ($t_{1/2,\beta}$) estimated by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"] in monkeys—13 hours for males, 11 hours for females—is essentially identical to the values estimated by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=2850396"]—10 or 15 hours for males (without/with outlier) and 8 hours in females. Hence the two studies appear consistent in identifying an initial elimination half-life, but the difference in design precluded Chengelis and colleagues from identifying the longer (terminal) half-life of PFBS.

1.3.5.4 Humans

In addition to their experimental studies in rats and monkeys, [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"] evaluated the elimination of human serum K^+PFBS in a group of workers with occupational exposure, with serum concentrations measured up to 180 days after cessation of further K^+PFBS work-related activity. Given that the workers had been occupationally exposed, distribution into the tissues is expected to have been complete before the observations began. The reported mean serum half-life was 23 days in males (n = 5) and 45.7 days in females (n = 1). Among the six subjects (five males, one female), the reported geometric mean serum elimination half-life for K^+PFBS was 25.8 days (95% confidence interval [CI]: 16.6–40.2 days). Because there was only one female subject, these data cannot be used to establish a significant sex difference in elimination. Urine appeared to be a major route of elimination in humans based on observed urine levels of PFBS in the study.

[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6781357"] also measured PFBS elimination in a study population with previous occupational exposure, in this case airport employees who were exposed to firefighting foam that contained PFBS. Eleven male and six female employees provided repeated blood samples during a period of observation with minimal exposure, and the data were analyzed with a linear mixed-effects pharmacokinetic model. The average half-life was 44 days (95% CI: 37–55 days). Although [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6781357"] evaluated age and sex as covariates of their statistical model, they did not report either as being a

significant factor for PFBS elimination. The average half-life (44 days) is larger than that reported by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"] (25.8 days), but there is significant overlap: the range of [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6781357"] is 21.6−87.2 days while the range of [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"] is 13.1−45.7 days.

For the sake of comparison, the linear mixed model used by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6781357"] was also applied to the estimated serum PFBS elimination half-life for the population and each individual worker (five male, one female) who manufactured K^+PFBS, described in [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"]. In brief, a linear mixed effect model is an extension of simple linear models that can be used to estimate toxicokinetic parameters such as the serum elimination rate constant (k_{elim}) and half-life by assuming one-compartment first-order elimination kinetics. The details of the linear mixed-effect model have been reported previously [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=4238434"]. Because of the limited sample size (only one female worker) and the lack of data on participant age for each worker in the study, age and sex were not included in the linear mixed model for reanalysis of the [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"] data, whereas both were included in [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6781357"]. In general, the estimated half-life using the linear mixed effect model were similar to originally reported values in [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"]. For instance, as compared with the reported average of 25.8 days ranging from 13.1−45.7 days [ADDIN EN.CITE <EndNote><Cite><Author>Olsen</Author><Year>2009</Year><RecNum>1045</RecNum><IDText>1326734</IDText><DisplayText>(Olsen et al., 2009)</DisplayText><record><rec-number>1045</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1045</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Olsen, G. W.</author><author>Chang, S. C.</author><author>Noker, P. E.</author><author>Gorman, G. S.</author><author>Ehresman, D. J.</author><author>Lieder, P. H.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>A comparison of the pharmacokinetics of perfluorobutanesulfonate (PFBS) in rats, monkeys, and humans</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>65-74</pages><volume>256</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>19059455</accession-

num><label>1326734</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2008.11.008</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2008.11.008</electronic-resource-num><language>English</language></record></Cite></EndNote>], the estimated population elimination half-life for serum PFBS was 25.0 days with individual estimates of 14.6–42.9 days using the linear mixed effect model.

Although the estimated serum half-lives of PFBS in [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"] overlapped with those of [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6781357"] (mean = 43.8 days, range = 21.9–87.6 days), there is a statistically significant difference between these two studies as suggested by both parametric (one-way analysis of variance [ANOVA]) and nonparametric analyses (Kruskal-Wallis test). Overall, the estimated serum half-life of PFBS by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6781357"] is about twofold higher than [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"].

Some of the difference between [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6781357"] and [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"] may be due to the difference in initial concentration, where the [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"] subjects had initial concentrations ranging from 100–1,000 ng/mL PFBS, while the highest initial concentrations in [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6781357"] was 1.3 ng/mL. It is possible that the higher serum levels in the [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"] subjects resulted in saturation of renal resorption, hence more rapid excretion/shorter half-lives. However, to the extent that some ongoing low-level exposure occurred during the period of observation, such exposure would cause a greater bias towards over-estimation of the elimination half-life for the [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6781357"] subjects than those of [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"]. The data of [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"] might also have a greater signal:noise ratio than the data of [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6781357"]. Despite this uncertainty, the fact that the blood concentrations of the [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6781357"] are more representative of environmental exposure, that their sample size was larger, and a significant statistical difference was observed, the two data sets will not be combined and the half-life estimated by [HYPERLINK

"https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6781357"] is presumed to better predict human dosimetry at environmental levels.

The possibility that menstrual blood loss could contribute to overall clearance was evaluated, assuming that the concentration of PFBS in menstrual blood is the same as in the general circulation and that the V_d in humans is equal to the average value estimated for monkeys (0.23 L/kg). The results indicate that this avenue of loss is more than two orders of magnitude slower than that indicated by the measured PFBS half-life in humans. Thus, menstrual blood loss is unlikely to contribute significantly to overall PFBS elimination.

1.3.6 Physiologically Based Pharmacokinetic Models

[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3223669"] developed a physiologically based pharmacokinetic model to estimate the concentration of PFAS, including PFBS, in human tissues based on an existing model and experimental data on concentrations of PFAS in human tissues from individuals in Catalonia, Spain. Several uncertainties in the model limit the use for this assessment of PFBS.

There are three chemical-specific parameters that determine the rate of elimination: the free fraction in blood, the maximum rate of resorption in the kidney (T_m), and the saturation constant for that resorption (K_t). No details beyond a rough description are provided on how these parameter values were identified. The data used for calibration are population samples in adults, who would essentially be at steady state, and only a single average level of exposure and corresponding blood concentration are reported, precluding the possibility of evaluating exposure or concentration dependence. In this situation it is not possible to uniquely identify the three parameters. This lack of identifiability is likely to be an underlying cause of the extreme variability in the individual parameter values (among the 11 PFAS evaluated) reported by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3223669"].

In addition, the rate constant for elimination from the glomerular filtrate compartment to the urine "storage" compartment (i.e., the bladder) is the total glomerular filtration rate (GFR), which is approximately 10 L/hour in a 70 kg adult. But most of the glomerular flow is resorbed in the nephrons, and human urinary output is less than 2 L/day. Hence, the use of GFR for elimination is not realistic. Finally, note that while the model structure and the equations listed by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3223669"] appear to be appropriate for most humans, excretion via lactation is not included.

Of considerable concern is the way in which partition coefficients (PCs) were identified. In particular, PCs were obtained by taking tissue concentration data from cadavers and comparing those to average blood concentrations from volunteer subjects, albeit from the same geographical area (county in Spain). The liver:blood PC for PFDA was thereby estimated to be 0.001 while the value for PFNA was 1.65. By contrast, [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5063958"] obtained values of ~0.6–0.7 for PFDA in male and female rats, ~1.2 for PFNA in male rats, and ~0.5 for PFNA in female rats. Thus, there seems to be extreme inconsistency and hence uncertainty in

these parameters as estimated by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3223669"]. Generally, human PCs should have values similar to those in rats.

The study authors do not compare model predictions for Tarragona County, Spain, with measured values for county residents (i.e., the data used for model calibration). Also, the study authors state that 20−30 years of simulated time are required to reach steady state. These steady-state estimates are inconsistent with the elimination data from [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"], in which the half-life in males was 24 days, and in one female subject 46 days. These empirical half-lives are consistent with a time to steady state of less than a year, indicating that the predicted clearance from [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3223669"] may be an order of magnitude or more too low. At the same time, the simulated levels of five PFAS (average levels) were consistently lower than the averages in the validation data, four of these being lower by an order of magnitude or more.

Thus, predictions of the [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3223669"] model are considered highly uncertain, and data other than those used by the study authors will be needed to accurately estimate key pharmacokinetic (PK) parameters for PFBS and these other PFAS, a task that would require significant additional research.

1.3.7 Summary

Collectively, elimination half-lives appear to be similar for mice and rats, with potential sex-specific toxicokinetic differences being reported (i.e., females appearing to have a faster elimination rate). Humans have a longer serum elimination half-life (~weeks) than both rodents (~hours) and monkeys (~days). Further, although V_d information is not available for humans, observations in male and female mice, rats, and monkeys exposed to comparable doses indicate comparability across species. Results of all studies discussed in this section are summarized in Table 2.

2.0 PROBLEM FORMULATION

2.1 CONCEPTUAL MODEL

A conceptual model was developed to summarize the availability of data to understand potential health hazards related to exposure to PFBS and/or K^+PFBS. The potential sources of these chemicals, the routes of exposure for biological receptors of concern (e.g., various human activities related to ingested drinking water, and food preparation and consumption), the potential organs and systems affected by exposure (e.g., effects such as developmental toxicity), and potential populations at risk due to exposure to PFBS and/or potassium salt are depicted in the conceptual diagram in [REF _Ref55818902 \h]. Arrows indicate linkage between one or more boxes between levels of organization.

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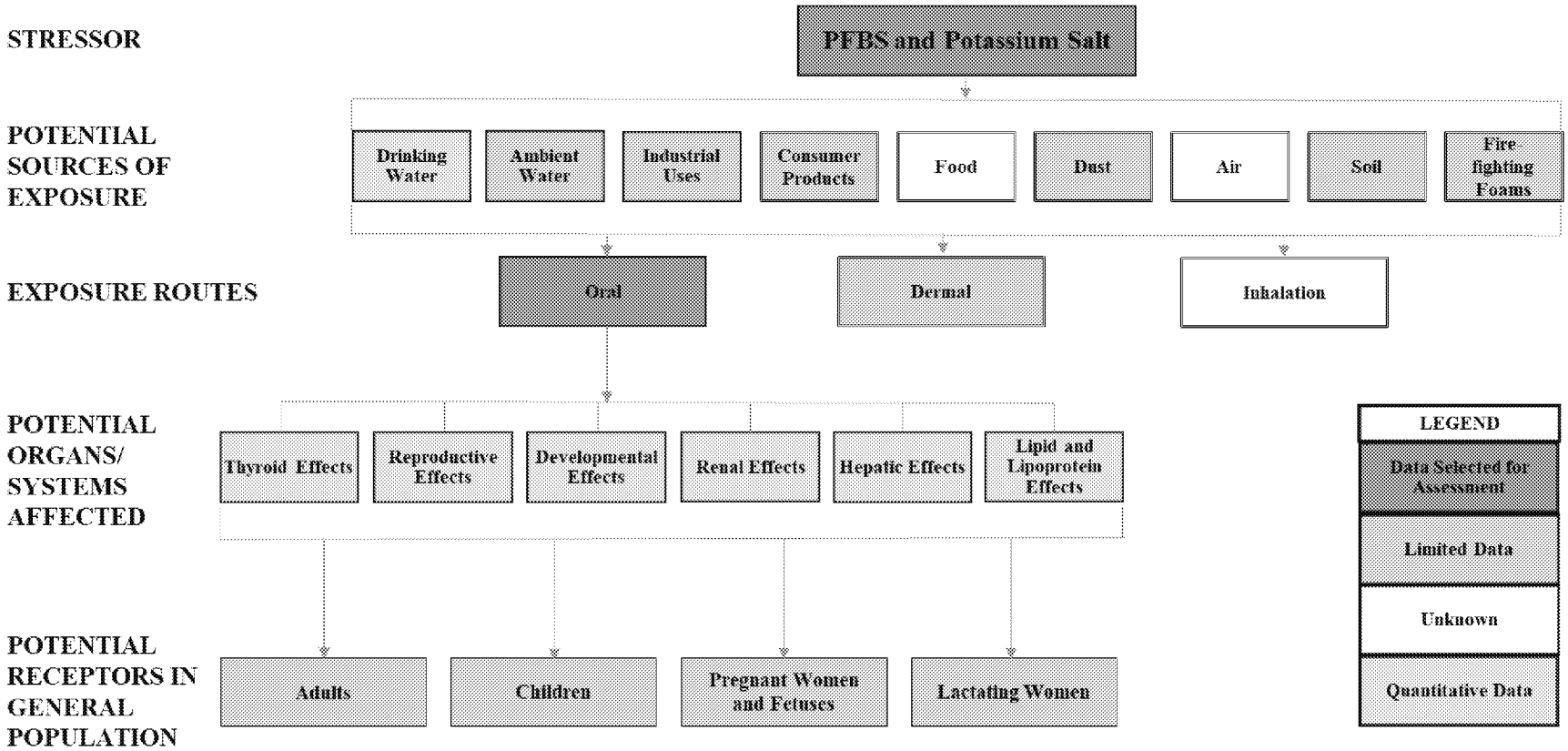

Figure [SEQ Figure * ARABIC]. Conceptual Model for PFBS and/or Potassium Salt

2.2 OBJECTIVE

The overall objective of this assessment is to provide the health effects basis for the development of oral reference doses (RfDs) for PFBS (CASRN 375-73-5) and its related compound K^+PFBS (CASRN 29420-49-3), including the science-based decisions providing the basis for identifying potential human health effects and estimating PODs. Based on the needs of the U.S. EPA partner program offices, regions, states, and/or tribes as they pertain to diverse exposure scenarios and human populations, subchronic and chronic RfDs have been derived. The assessment includes studies and information previously provided in the 2014 PPRTV assessment [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2014</Year><RecNum>1274</RecNum><IDText>3981183</IDText><DisplayText>(U.S. EPA, 2014f)</DisplayText><record><rec-number>1274</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1274</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Provisional peer-reviewed toxicity values for perfluorobutane sulfonate (CASRN 375-73-5) and related compound potassium perfluorobutane sulfonate (CASRN 29420-49-3)</title></titles><dates><year>2014</year></dates><isbn>EPA/690/R-14/012F</isbn><label>3981183</label><work-type>EPA Report</work-type><urls><related-urls><url>https://hhpprtv.ornl.gov/issue_papers/PerfluorobutanesulfonicacidPFBS.pdf</url></related-urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>] and builds upon data from the literature published since that review.

2.3 METHODS

2.3.1 Literature Search

Four online scientific databases (PubMed, Web of Science, TOXLINE, and TSCATS via TOXLINE) were searched by the U.S. EPA's Health and Environmental Research Online (HERO) staff and stored in the HERO database.[5] The literature search focused on chemical name and synonyms with no limitations on publication type, evidence stream (i.e., human, animal, in vitro, and in silico), or health outcomes. Full details of the search strategy for each database are presented in Appendix A. The initial database searches were conducted on July 18, 2017 and updated on February 28, 2018; May 1, 2019; and May 15, 2020. Additional studies [e.g., [ADDIN EN.CITE ADDIN EN.CITE.DATA]] were identified during subsequent review periods and integrated into the assessment as appropriate. Studies were also identified from other sources relevant to PFBS, including studies submitted to the U.S. EPA by the manufacturer of PFBS (i.e., 3M) as part of the Toxic Substances Control Act (TSCA) premanufacture notices for other PFAS chemicals or as required under TSCA reporting requirements and studies referenced in prior evaluations of PFBS toxicity [ADDIN EN.CITE <EndNote><Cite><Author>ATSDR</Author><Year>2015</Year><RecNum>1283</RecNum><IDText>3859918</IDText><DisplayText>(MDH, 2020; ATSDR, 2015)</DisplayText><record><rec-number>1283</rec-number><foreign-keys><key app="EN"

[5]The U.S. EPA's HERO database provides access to the scientific literature behind U.S. EPA science assessments. The database includes more than 2,500,000 scientific references and data from the peer-reviewed literature used by the U.S. EPA to develop its regulations.

db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt"
timestamp="1604957801">1283</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ATSDR,</author></authors></contributors><titles><title>Draft toxicological profile for perfluoroalkyls</title></titles><dates><year>2015</year></dates><label>3859918</label><urls><related-urls><url>https://www.atsdr.cdc.gov/toxprofiles/tp200.pdf</url></related-urls></urls><language>English</language><modified-date>Agency for Toxic Substances and Disease Registry</modified-date></record></Cite><Cite><Author>MDH</Author><Year>2020</Year><RecNum>580</RecNum><record><rec-number>580</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604955591">580</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>MDH,</author></authors></contributors><titles><title>Toxicological summary for: Perfluorobutane sulfonate</title></titles><dates><year>2020</year></dates><publisher>Minnesota Department of Health, Health Based Guidance for Water Health Risk Assessment Unit, Environmental Health Division</publisher><label>4409296</label><urls><related-urls><url>https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfbssummary.pdf</url></related-urls></urls><language>English</language><modified-date>Minnesota Department of Health</modified-date></record></Cite></EndNote>]. In addition, on March 29, 2018, the National Toxicology Program (NTP) published study tables and individual animal data from a 28-day toxicity study of PFBS ([HYPERLINK "http://doi.org/10.22427/NTP-DATA-002-01134-0003-0000-4"]), with a protocol outlining the NTP study methods available in HERO ([HYPERLINK "https://hero.epa.gov/hero/index.cfm/reference/details/reference_id/4309741"]) [ADDIN EN.CITE <EndNote><Cite><Author>NTP</Author><Year>2011</Year><RecNum>1255</RecNum><IDText>4309741</IDText><DisplayText>(NTP, 2011)</DisplayText><record><rec-number>1255</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1255</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NTP,</author></authors></contributors><titles><title>NTP Protocol Outline of the Class Study of Perfluorinated Chemicals [perfluorobutane sulfonate (PFBS), perfluorohexane sulfonate potassium salt (PFHSKslt), perfluorooctane sulfonate (PFOS), perfluorohexanoic acid (PFHxA), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA) and WY 14643 (WY)] in Harlan Sprague Dawley rats administered daily by gavage for 28-Days</title></titles><dates><year>2011</year></dates><label>4309741</label><work-type>NTP</work-type><urls></urls><language>English</language><modified-date>National Toxicology Program</modified-date></record></Cite></EndNote>]. The final *NTP Technical Report on the Toxicity Studies of Perfluoroalkyl Sulfonates Administered by Gavage to Sprague-Dawley Rats* was published in August, 2019 [ADDIN EN.CITE <EndNote><Cite><Author>NTP</Author><Year>2019</Year><RecNum>1223</RecNum><IDText>5400978</IDText><DisplayText>(NTP, 2019)</DisplayText><record><rec-number>1223</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1223</key></foreign-

keys><ref-type name="Report">27</ref-type><contributors><authors><author>NTP,</author></authors></contributors><titles><title> NTP technical report on the toxicity studies of perfluoroalkyl sulfonates (perfluorobutane sulfonic acid, perfluorohexane sulfonate potassium salt, and perfluorooctane sulfonic acid) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats</title></titles><dates><year>2019</year></dates><pub-location>Research Triangle Park, NC</pub-location><isbn>Toxicity Report 96</isbn><label>5400978</label><urls><related-urls><url>https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox096_508.pdf</url></related-urls></urls><language>English</language><modified-date>National Toxicology Program</modified-date></record></Cite></EndNote>].

2.3.2 Screening Process

Two screeners independently conducted a title and abstract screening of the search results using [HYPERLINK "https://www.evidencepartners.com/products/distillersr-systematic-review-software"][6] to identify study records that met the Population, Exposure, Comparator, and Outcome (PECO) eligibility criteria (see Appendix B for a more detailed summary):

- Population: Human and nonhuman mammalian animal species (whole organism) of any life stage and in vitro models of genotoxicity.
- Exposure: Any qualitative or quantitative estimates of exposure of PFBS or K^+PFBS, via oral or inhalation routes of exposure. (Note: Nonoral and noninhalation studies are tracked as potential supplemental material and are presented in Section [REF _Ref54957982 \r \h].)
- Comparator: A comparison or reference population exposed to lower levels or for shorter periods of time for humans. Exposure to vehicle-only or untreated control in animals.
- Outcome: Any examination of cancer or noncancer health outcomes.

In addition to the PECO criteria, the following additional exclusion criteria were applied, although these study types were tracked as supplemental material as described following the exclusion criteria:

- Records that do not contain original data such as other agency assessments, scientific literature reviews, editorials, and commentaries;
- Abstract only (e.g., conference abstracts); and
- Retracted studies.

Records that were not excluded based on title and abstract screening advanced to full-text review using the same PECO eligibility criteria. Studies that have not undergone peer review were included if the information could be made public and sufficient details of study methods and findings were included in the reports. Full-text copies of potentially relevant records identified from title and abstract screening were retrieved, stored in the HERO database, and independently assessed by the screeners using DistillerSR to confirm eligibility. At both title/abstract and full-text review levels, screening conflicts were resolved by discussion between

[6][HYPERLINK "https://www.evidencepartners.com/products/distillersr-systematic-review-software"] is a web-based systematic review software used to screen studies available at [HYPERLINK "https://www.evidencepartners.com/products/distillersr-systematic-review-software"].

the primary screeners in consultation with a third reviewer to resolve any remaining disagreements. During title/abstract or full-text level screening, studies that were not directly relevant to the PECO, but could provide supplemental information, were categorized (or "tagged") by the type of supplemental information they provided (e.g., review, commentary, or letter with no original data; conference abstract; toxicokinetics; mechanistic information aside from in vitro genotoxicity studies; other routes of exposure; exposure only). Conflict resolution was not required during the screening process to identify supplemental information (i.e., tagging by a single screener was sufficient to identify the study as potential supplemental information).

2.3.3 Study Evaluation

Study evaluation was conducted by one reviewer for epidemiological studies and by two independent reviewers for animal studies using the U.S. EPA's version of Health Assessment Workspace Collaborative (HAWC), a free and open source web-based software application designed to manage and facilitate the process of conducting literature assessments.[7] For pragmatic purposes, only one reviewer was considered necessary for epidemiological studies because it was apparent during literature screening that the animal evidence would be the most informative for deriving toxicity values. The available outcomes in the epidemiological studies were heterogeneous and unrelated to each other, and only a single study was available for each outcome. This approach is consistent with recommendations from the National Academies of Science encouraging the U.S. EPA to explore ways to make systematic review more feasible, including a "rapid review in which components of the systematic review process are simplified or omitted (e.g., the need for two independent reviewers)" [ADDIN EN.CITE <EndNote><Cite><Author>NASEM</Author><Year>2017</Year><RecNum>1272</RecNum><IDText>3982546</IDText><DisplayText>(NASEM, 2017)</DisplayText><record><rec-number>1272</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1272</key></foreign-keys><ref-type name="Book">6</ref-type><contributors><authors><author>NASEM,</author></authors></contributors><titles><title>Application of systematic review methods in an overall strategy for evaluating low-dose toxicity from endocrine active chemicals</title></titles><pages>180</pages><dates><year>2017</year></dates><pub-location>Washington, D.C.</pub-location><publisher>The National Academies Press</publisher><label>3982546</label><urls><related-urls><url>http://dx.doi.org/10.17226/24758</url></related-urls></urls><electronic-resource-num>10.17226/24758</electronic-resource-num><language>English</language><modified-date>National Academies of Sciences, Engineering, and Medicine</modified-date></record></Cite></EndNote>]. Study evaluation was not conducted for studies tagged during screening as supplemental information.

The general approach for evaluating epidemiology and animal toxicology was the same (see [REF _Ref55814427 \h]), but the specifics of applying the approach differed. These evaluations were focused on the methodological approaches and completeness of reporting in the individual studies, rather than on the direction or magnitude of the study results. Evaluation of epidemiology studies was conducted for the following domains: exposure measures, outcome

[7]HAWC: A modular web-based interface to facilitate development of human health assessments of chemicals ([HYPERLINK "https://hawcproject.org/"]).

measures, participant selection, confounding, analysis, sensitivity, and selective reporting. For animal studies, the evaluation process focused on assessing aspects of the study design and conduct through three broad types of evaluations: reporting quality, risk of bias, and study sensitivity. A set of domains with accompanying core questions fall under each evaluation type and directed individual reviewers to evaluate specific study characteristics. For each domain evaluated for experimental animal studies (reporting quality, selection or performance bias, confounding/variable control, reporting or attrition bias, exposure methods sensitivity, and outcome measures and results display), basic considerations provided additional guidance on how a reviewer might evaluate and judge a study for that domain. Core and prompting questions used to guide the criteria and judgment for each domain are presented in Appendix C. Key concerns for the review of epidemiology and animal toxicology studies are potential sources of bias (factors that could systematically affect the magnitude or direction of an effect in either direction) and insensitivity (factors that limit the ability of a study to detect a true effect).

For each study in each evaluation domain, reviewers reached a consensus rating regarding the utility of the study for hazard identification, with categories of *good*, *adequate*, *deficient*, *not reported,* or *critically deficient*. These ratings were then combined across domains to reach an overall classification of *high*, *medium*, or *low confidence* or *uninformative* (definitions of these classifications are available in Appendix C). The rationale for the classification, including a brief description of any identified strengths and/or limitations from the domains and their potential impact on the overall confidence determination, is documented and retrievable in HAWC. Uninformative studies were not used in evidence synthesis or dose-response analysis. Studies were evaluated for their suitability for each health outcome investigated and could receive different ratings for each outcome.

For epidemiological studies, exposure-specific criteria were developed prior to evaluation and are described in detail in Appendix C. In brief, standard analytical methods of measurement of PFBS in serum or whole-blood using quantitative techniques such as liquid chromatograph-triple quadrupole mass spectrometry and high-pressure liquid chromatography with tandem mass spectrometry were preferred. In addition, exposure must have been assessed in a relevant time window for development of the outcome.

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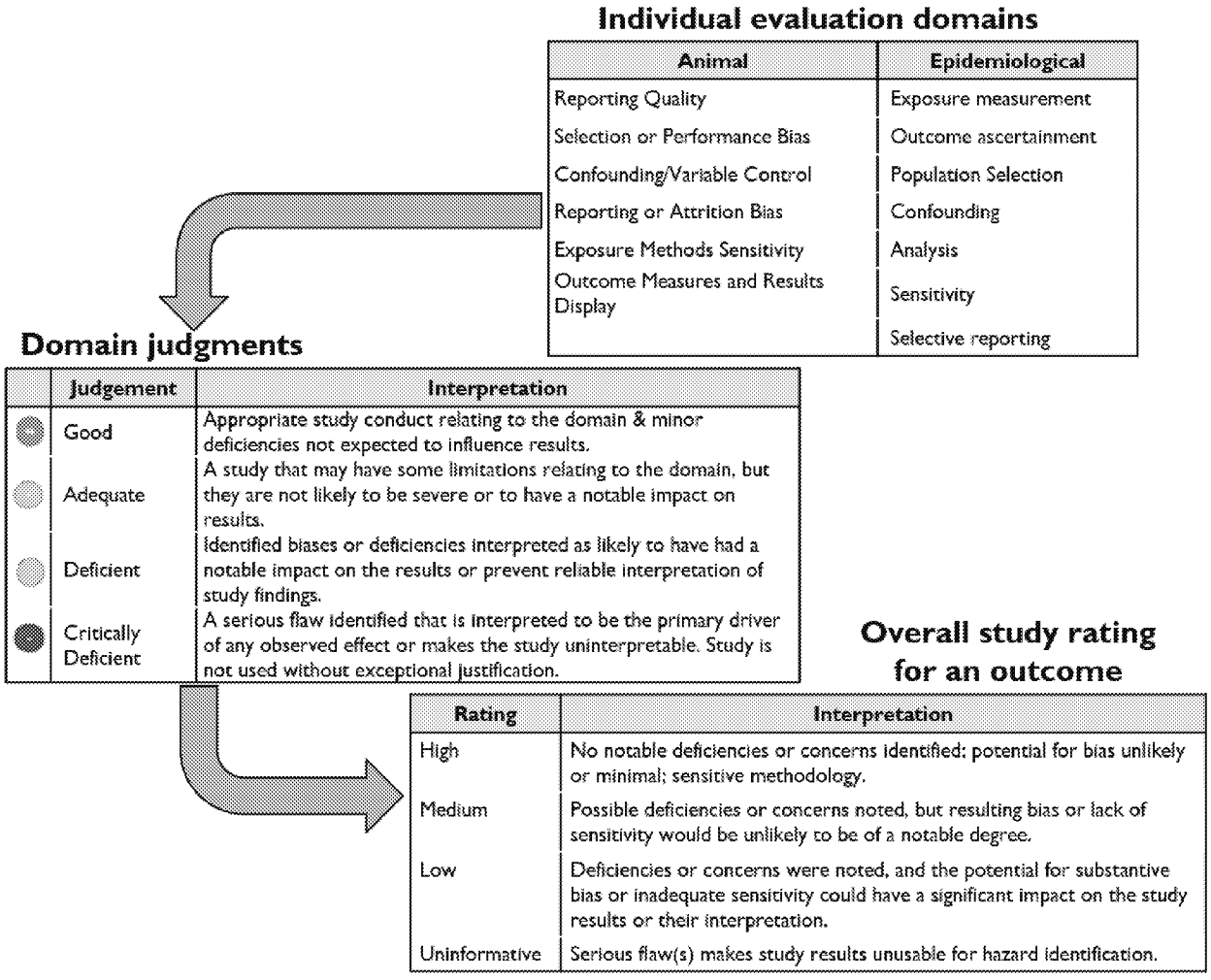

Figure [SEQ Figure * ARABIC]. Approach for Evaluating Epidemiological and Animal Toxicology Studies

2.3.4 Data Extraction

Information on study design, methods, results, and data from animal toxicology studies were extracted into the HAWC and are available at [HYPERLINK "https://hawcprd.epa.gov/assessment/100000037/"]. Visual graphics prepared from HAWC are embedded as hyperlinks and are fully interactive when viewed online by way of a "click to see more" capability. Clicking on content allows access to study evaluation ratings, methodological details, and underlying study data. The action of clicking on content contained in those visual graphics (e.g., data points, endpoint, and study design) will yield the underlying data supporting the visual content.[8] A HAWC user guide can be found in Appendix D. Study methods and findings from epidemiological studies were described in narratives, given the small size and heterogeneity of the evidence base. Data extraction was performed by one member of the

[8]The following browsers are fully supported for accessing HAWC: Google Chrome (preferred), Mozilla Firefox, and Apple Safari. There are errors in functionality when viewed with Internet Explorer.

evaluation team and checked by one to two other members. Any discrepancies in data extraction were resolved by discussion or consultation with a third member of the evaluation team. Digital rulers such as WebPlotDigitizer and Grab It! ([HYPERLINK "https://automeris.io/WebPlotDigitizer/"] and [HYPERLINK "https://grab-it.soft112.com/"], respectively) were used to extract numerical information from figures. Use of digital rulers was documented during extraction. Dose levels were extracted as reported in the study and converted to mg/kg-day (HED) for endpoints that were considered for use in the dose-response and derivation of toxicity values.

2.3.5 Evidence Synthesis

For the purposes of this assessment, after study evaluation, the informative evidence for each outcome was summarized from the available human studies and, separately, the available animal studies. This synthesis provides a short synopsis of the breadth of data available to inform each outcome and summarizes information on the general study design, doses tested, outcomes evaluated, and results for the endpoints of interest within each study. While the evidence synthesis describes inferences about the methodological rigor and sensitivity of the individual studies (i.e., study confidence) and discusses the pattern and magnitude of the experimental findings within studies, it does not include conclusions drawn across the sets of studies (see "Evidence Integration and Hazard Characterization," next).

2.3.6 Evidence Integration and Hazard Characterization

In this assessment, the evaluation of the available evidence from informative human and animal studies was described in an evidence integration narrative for each outcome, including overall evidence integration judgments as to whether the data provide evidence sufficient to support a hazard. These integrated judgments serve to characterize the extent of the available evidence for each outcome, including information on potential susceptible populations and life stages, as well as important uncertainties in interpreting the data.

The evidence integration for each health effect considered aspects of an association that might suggest causation first introduced by Austin Bradford Hill [ADDIN EN.CITE <EndNote><Cite><Author>Hill</Author><Year>1965</Year><RecNum>1000</RecNum><IDText>71664</IDText><DisplayText>(Hill, 1965)</DisplayText><record><rec-number>1000</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1000</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Hill, A. B.</author></authors></contributors><titles><title>The environment and disease: Association or causation?</title><secondary-title>Proceedings of the Royal Society of Medicine</secondary-title><alt-title>Proc R Soc Med</alt-title><short-title>Proceedings of the Royal Society of Medicine</short-title></titles><periodical><full-title>Proceedings of the Royal Society of Medicine</full-title><abbr-1>Proc R Soc Med</abbr-1></periodical><alt-periodical><full-title>Proceedings of the Royal Society of Medicine</full-title><abbr-1>Proc R Soc Med</abbr-1></alt-periodical><pages>295-300</pages><volume>58</volume><number>5</number><dates><year>1965</year></dates><isbn>ISSN 0035-9157</isbn><accession-num>14283879</accession-num><label>71664</label><urls></urls><language>English</language></record></Cite></EndNote>], including the consistency, exposure-response relationship, strength of association,

biological plausibility, and coherence of the evidence. This involved weighing the PFBS-specific human and animal evidence relating to each of these considerations within or across studies, including both evidence that supports causation as well as evidence that indicates lack of support. For example, the evaluation of consistency examined the similarity of results across studies (e.g., direction and magnitude). When inconsistencies across studies were identified, the evaluation considered whether results were "conflicting" (i.e., unexplained positive and negative results in similarly exposed human populations or in similar animal models) or "differing" (i.e., mixed results explained by differences between human populations, animal models, exposure conditions, or study methods), based on analyses of potentially important explanatory factors such as confidence in the studies' results (the results of higher confidence studies were emphasized), exposure levels or duration, or differences in populations or species (including potential susceptible groups) across studies [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2005</Year><RecNum>1222</RecNum><IDText>6324329</IDText><DisplayText>(U.S. EPA, 2005)</DisplayText><record><rec-number>1222</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1222</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Guidelines for carcinogen risk assessment</title></titles><dates><year>2005</year></dates><pub-location>Washington, DC</pub-location><publisher>U.S. Environmental Protection Agency, Risk Assessment Forum</publisher><isbn>EPA/630/P-03/001B</isbn><label>6324329</label><work-type>EPA Report</work-type><urls><related-urls><url>https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf</url></related-urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>]. While consistent evidence across studies increases support for a hazard, unexplained inconsistency or conflicting evidence decreases support for a hazard. The evaluations of these considerations were informed by U.S. EPA guidelines, including *Guidelines for Developmental Toxicity Risk Assessment* [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>1991</Year><RecNum>938</RecNum><IDText>732120</IDText><DisplayText>(U.S. EPA, 1991a)</DisplayText><record><rec-number>938</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">938</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Guidelines for developmental toxicity risk assessment</title><secondary-title>Federal Register</secondary-title><alt-title>Fed. Reg.</alt-title><short-title>Federal Register</short-title></titles><periodical><full-title>Federal Register</full-title><abbr-1>Fed. Reg.</abbr-1></periodical><alt-periodical><full-title>Federal Register</full-title><abbr-1>Fed. Reg.</abbr-1></alt-periodical><pages>63798-63826</pages><volume>56</volume><number>234</number><dates><year>1991</year></dates><isbn>ISSN 0097-6326
EISSN 2167-2520</isbn><label>732120</label><urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>] and *Guidelines for Reproductive Toxicity Risk Assessment* [ADDIN EN.CITE <EndNote><Cite><Author>U.S.

EPA</Author><Year>1996</Year><RecNum>1319</RecNum><IDText>30019</IDText><DisplayText>(U.S. EPA, 1996a)</DisplayText><record><rec-number>1319</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1319</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Guidelines for reproductive toxicity risk assessment</title></titles><pages>1-143</pages><dates><year>1996</year></dates><pub-location>Washington, DC</pub-location><publisher>U.S. Environmental Protection Agency, Risk Assessment Forum</publisher><isbn>EPA/630/R-96/009</isbn><label>30019</label><urls><related-urls><url>https://www.epa.gov/sites/production/files/2014-11/documents/guidelines_repro_toxicity.pdf</url></related-urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>].

The overall evidence integration judgments were developed using a structured framework based on evaluation of the considerations above (see [REF _Ref55818017 \h]). Using this framework, the human and animal evidence for each health effect was judged separately as *supports a hazard*, *equivocal*, or *supports no hazard*. Evidence integration judgments of *supports a hazard* span a range of supportive evidence bases that can be further differentiated by the quantity and quality of information available to rule out alternative explanations for the results. *Equivocal* evidence is limited in terms of the quantity, consistency, or confidence level of the available studies and serves to encourage additional research. *Supports no hazard* requires several high-confidence studies across potentially susceptible populations with consistent null results; this judgment was not reached in this assessment. Overall evidence integration judgments were made based on conclusions from both the animal and human data, considering the available information on the human relevance of findings in animals. Thus, for example, evidence in animals that *supports a hazard* alongside *equivocal* human evidence in the absence of information indicating that the responses in animals are unlikely to be relevant to humans would result in an overall judgment of *supports a hazard* for that outcome.

Table [SEQ Table * ARABIC]. Criteria for Overall Evidence Integration Judgments

	Animal	Human
Supports a hazard	The evidence for effects is consistent or largely consistent in at least one high- or medium-confidence experiment.[a] Although notable uncertainties across studies might remain, any inconsistent evidence or remaining uncertainties are insufficient to discount the cause for concern from the positive experiments. In the strongest scenarios, the set of experiments provide evidence supporting a causal association across independent laboratories or species. In other scenarios, including evidence for an effect in a single study, the experiment(s) demonstrate additional support for causality such as coherent effects across multiple related endpoints; an unusual magnitude of effect, rarity, age at onset, or severity; a strong dose-response relationship; and/or consistent observations across exposure scenarios (e.g., route, timing, or duration), sexes, or animal strains.	One or more high- or medium-confidence independent studies reporting an association between the exposure and the health outcome. In general, the study results are largely consistent or any inconsistent results are insufficient to discount the cause for concern from the higher confidence study or studies, and there is reasonable confidence that alternative explanations, including chance, bias, and confounding, have been ruled out. In situations in which only a single study is available, the results of multiple studies are heterogeneous, or alternative explanations, including chance, bias and confounding, have not been ruled out, there is additional supporting evidence such as associations with biologically related endpoints in other human studies (coherence), large estimates of risk, or strong evidence of an exposure-response within or across studies.
Equivocal	The evidence is generally inadequate to determine hazard. This includes a lack of relevant studies available or a set of low-confidence experiments. It also includes scenarios with a set of high- or medium-confidence experiments that are not reasonably consistent or not considered informative to the hazard question under evaluation. This category would also include a single high- or medium-confidence experiment with weak evidence of an effect (e.g., changes in one endpoint among several related endpoints, and without additional evidence supporting causality).	The evidence is considered inadequate to describe an association between exposure and the health outcome with confidence. This includes a lack of studies available in humans, only low-confidence studies, or considerable heterogeneity across medium- or high-confidence studies. This also includes scenarios in which there are serious residual uncertainties across studies (these uncertainties typically relate to exposure characterization or outcome ascertainment, including temporality) in a set of largely consistent medium- or high-confidence studies.
Supports no hazard	A set of high-confidence experiments examining the full spectrum of related endpoints within a type of toxicity, with multiple species, and testing a reasonable range of exposure levels and adequate sample size in both sexes, with none showing any indication of effects. The data are compelling in that the experiments have examined the range of scenarios across which health effects in animals could be observed, and an alternative explanation (e.g., inadequately controlled features of the studies' experimental designs) for the observed lack of effects is not available. The experiments were designed to specifically test for effects of interest, including suitable exposure timing and duration, post-exposure latency, and endpoint evaluation procedures, and to address potentially susceptible populations and life stages.	Several high-confidence studies, showing consistently null results (e.g., an OR of 1.0) ruling out alternative explanations including chance, bias, and confounding with reasonable confidence. Each of the studies should have used an optimal outcome and exposure assessment and adequate sample size (specifically for higher exposure groups and for sensitive populations). The set as a whole should include the full range of levels of exposures that human beings are known to encounter, an evaluation of an exposure response gradient, and at-risk populations and life stages and should be mutually consistent in not showing any indication of effect at any level of exposure.

Table [SEQ Table * ARABIC]. Criteria for Overall Evidence Integration Judgments		
	Animal	Human

[a]"Experiment" refers to measurements in a single population of exposed animals (e.g., a study that included separate evaluations of rats and of mice, or separate cohorts exposed at different life stages, would be considered as multiple experiments). Conversely, two papers or studies that report on the same cohort of exposed animals (e.g., examining different endpoints) would not be considered separate experiments.

OR = odds ratio.

The primary evidence and rationale supporting these decisions were summarized in a single evidence profile table to transparently convey the aspects of the evidence that were considered to increase or decrease the hazard support for each health effect. For the purposes of this assessment, only the integrated evidence that *supports a hazard* was considered for use in the dose-response analysis and derivation of toxicity values.

2.3.7 Derivation of Values

Development of the dose-response assessment for PFBS and/or the potassium salt has followed the general guidelines for risk assessment put forth by the National Research Council [ADDIN EN.CITE <EndNote><Cite><Author>NRC</Author><Year>1983</Year><RecNum>1314</RecNum><IDText>194806</IDText><DisplayText>(NRC, 1983)</DisplayText><record><rec-number>1314</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1314</key></foreign-keys><ref-type name="Book">6</ref-type><contributors><authors><author>NRC,</author></authors></contributors><titles><title>Risk assessment in the federal government: Managing the process</title></titles><dates><year>1983</year></dates><pub-location>Washington, DC</pub-location><publisher>National Academy Press</publisher><accession-num>25032414</accession-num><label>194806</label><urls><related-urls><url>http://dx.doi.org/10.17226/366</url></related-urls></urls><electronic-resource-num>10.17226/366</electronic-resource-num><language>English</language><modified-date>National Research Council</modified-date></record></Cite></EndNote>] and the U.S. EPA's *Framework for Human Health Risk Assessment to Inform Decision Making* [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2014</Year><RecNum>1301</RecNum><IDText>2324779</IDText><DisplayText>(U.S. EPA, 2014c)</DisplayText><record><rec-number>1301</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1301</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Framework for human health risk assessment to inform decision making. Final</title></titles><dates><year>2014</year></dates><pub-location>Washington, DC</pub-location><publisher>U.S. Environmental Protection, Risk Assessment Forum</publisher><isbn>EPA/100/R-14/001</isbn><label>2324779</label><work-type>EPA

Report</work-type><urls><related-urls><url>https://www.epa.gov/risk/framework-human-health-risk-assessment-inform-decision-making</url></related-urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>]. Other U.S. EPA guidelines and reviews considered in the development of this assessment include the following:

- *A Review of the Reference Dose and Reference Concentration Processes* [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2002</Year><RecNum>1316</RecNum><IDText>88824</IDTe xt><DisplayText>(U.S. EPA, 2002)</DisplayText><record><rec-number>1316</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1316</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>A review of the reference dose and reference concentration processes</title></titles><dates><year>2002</year></dates><pub-location>Washington, DC</pub-location><publisher>U.S. Environmental Protection Agency, Risk Assessment Forum</publisher><isbn>EPA/630/P-02/002F</isbn><label>88824</label><urls><related-urls><url>https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf</url></related-urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>].
- *A Framework for Assessing Health Risks of Environmental Exposures to Children* [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2006</Year><RecNum>1315</RecNum><IDText>194567</IDT ext><DisplayText>(U.S. EPA, 2006)</DisplayText><record><rec-number>1315</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1315</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>A framework for assessing health risk of environmental exposures to children</title></titles><pages>1-145</pages><dates><year>2006</year></dates><pub-location>Washington, DC</pub-location><publisher>U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment</publisher><isbn>EPA/600/R-05/093F</isbn><label>194567</label><urls><related-urls><url>http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=158363</url></related-urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>].
- *Exposure Factors Handbook* [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2011</Year><RecNum>1310</RecNum><IDText>786546</IDT ext><DisplayText>(U.S. EPA, 2011a)</DisplayText><record><rec-number>1310</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1310</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S.

EPA,</author></authors></contributors><titles><title>Exposure factors handbook: 2011 edition</title></titles><dates><year>2011</year></dates><pub-location>Washington, DC</pub-location><isbn>EPA/600/R-090/052F</isbn><label>786546</label><work-type>EPA Report</work-type><urls><related-urls><url>http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=236252</url></related-urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>].[9]

- *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2011</Year><RecNum>1311</RecNum><IDText>752972</IDT ext><DisplayText>(U.S. EPA, 2011b)</DisplayText><record><rec-number>1311</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1311</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Recommended use of body weight 3/4 as the default method in derivation of the oral reference dose</title></titles><pages>1-50</pages><dates><year>2011</year></dates><pub-location>Washington, DC</pub-location><publisher>U.S. Environmental Protection Agency, Risk Assessment Forum, Office of the Science Advisor</publisher><isbn>EPA/100/R-11/0001</isbn><label>752972</label><urls><related-urls><url>https://www.epa.gov/sites/production/files/2013-09/documents/recommended-use-of-bw34.pdf</url></related-urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>].
- *Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation* [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2014</Year><RecNum>1300</RecNum><IDText>2520260</ID Text><DisplayText>(U.S. EPA, 2014d)</DisplayText><record><rec-number>1300</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1300</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Guidance for applying quantitative data to develop data-derived extrapolation factors for interspecies and intraspecies extrapolation</title></titles><dates><year>2014</year></dates><pub-location>Washington, DC</pub-location><publisher>Risk Assessment Forum, Office of the Science Advisor</publisher><isbn>EPA/100/R-14/002F</isbn><label>2520260</label><work-type>EPA Report</work-type><urls><related-urls><url>https://www.epa.gov/sites/production/files/2015-01/documents/ddef-final.pdf</url></related-

[9]Please note that specific updates to this handbook are available at [HYPERLINK "https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252"].

urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>].

- *Benchmark Dose Technical Guidance Document* [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2012</Year><RecNum>1309</RecNum><IDText>1239433</IDText><DisplayText>(U.S. EPA, 2012)</DisplayText><record><rec-number>1309</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1309</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Benchmark dose technical guidance</title></titles><dates><year>2012</year></dates><pub-location>Washington, DC</pub-location><publisher>U.S. Environmental Protection Agency, Risk Assessment Forum</publisher><isbn>EPA/100/R-12/001</isbn><label>1239433</label><urls><related-urls><url>https://www.epa.gov/risk/benchmark-dose-technical-guidance</url></related-urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>].
- *Child-Specific Exposure Scenarios Examples* [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2014</Year><RecNum>1299</RecNum><IDText>2770491</IDText><DisplayText>(U.S. EPA, 2014a)</DisplayText><record><rec-number>1299</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1299</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Child-specific exposure scenarios examples</title></titles><dates><year>2014</year></dates><pub-location>Washington, DC</pub-location><isbn>EPA/600/R-14/217F</isbn><label>2770491</label><work-type>EPA Report</work-type><urls><related-urls><url>http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=262211</url></related-urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>].

The U.S. EPA's *A Review of the Reference Dose and Reference Concentration Processes* describes a multistep approach to dose–response assessment, including analysis in the range of observation followed by extrapolation to lower levels [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2002</Year><RecNum>1316</RecNum><IDText>88824</IDText><DisplayText>(U.S. EPA, 2002)</DisplayText><record><rec-number>1316</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1316</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>A review of the reference dose and reference concentration processes</title></titles><dates><year>2002</year></dates><pub-location>Washington, DC</pub-location><publisher>U.S. Environmental Protection Agency, Risk Assessment Forum</publisher><isbn>EPA/630/P-

02/002F</isbn><label>88824</label><urls><related-urls><url>https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf</url></related-urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>]. As described above, before deriving toxicity values, the U.S. EPA conducted a comprehensive evaluation of available human epidemiological and animal toxicity studies to identify potential health hazards and associated dose-response information through the literature search and screening, study evaluation, evidence synthesis, and evidence integration steps. This evaluation informed the selection of candidate key studies and critical effects for dose-response analysis, from which the U.S. EPA identified a critical effect and point of departure (POD) for subchronic and chronic reference value derivation and extrapolated a selected POD to a corresponding RfD (e.g., subchronic RfD). For dose-response analysis of PFBS and/or the potassium salt, the U.S. EPA used the BMD approach to identify a POD. The steps for deriving an RfD using the BMD approach are summarized below.

- **Step 1: Evaluate the data to identify and characterize endpoints related to exposure to PFBS chemicals.** This step involved determining the relevant studies and adverse effects to be considered for BMD modeling. Once the appropriate data were collected, evaluated for study quality, and characterized for adverse outcomes, endpoints were selected that were judged to be relevant (i.e., for the purposes of this assessment, effects that were sufficient to *support a hazard*) and sensitive as a function of dose (typically defined by the no-observed-adverse-effect level [NOAEL] value). In this assessment, these decisions were directly informed by the evidence integration judgments arrived at for each assessed health outcome. Some of the most important considerations that influenced selection of endpoints for BMD modeling include data showing a dose-response relationship, percent change from controls, adversity of effect, and consistency across studies. For PFBS, thyroid, developmental, and kidney endpoints were considered for toxicity value derivations.
- **Step 2: Convert the adjusted daily doses to an HED.** The adjusted daily doses were converted to HEDs by considering U.S. EPA's *Recommended Use of Body Weight*$^{3/4}$ *as the Default Method in Derivation of the Oral Reference Dose* [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2011</Year><RecNum>1311</RecNum><IDText>752972</IDT ext><DisplayText>(U.S. EPA, 2011b)</DisplayText><record><rec-number>1311</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1311</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Recommended use of body weight 3/4 as the default method in derivation of the oral reference dose</title></titles><pages>1-50</pages><dates><year>2011</year></dates><pub-location>Washington, DC</pub-location><publisher>U.S. Environmental Protection Agency, Risk Assessment Forum, Office of the Science Advisor</publisher><isbn>EPA/100/R-11/0001</isbn><label>752972</label><urls><related-urls><url>https://www.epa.gov/sites/production/files/2013-09/documents/recommended-use-of-bw34.pdf</url></related-urls></urls><language>English</language><modified-

date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>].

- **Step 3: Select the benchmark response (BMR) level.** The endpoints selected were modeled using the U.S. EPA's *Benchmark Dose Technical Guidance Document* [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2012</Year><RecNum>1309</RecNum><IDText>1239433</IDText><DisplayText>(U.S. EPA, 2012)</DisplayText><record><rec-number>1309</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1309</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Benchmark dose technical guidance</title></titles><dates><year>2012</year></dates><pub-location>Washington, DC</pub-location><publisher>U.S. Environmental Protection Agency, Risk Assessment Forum</publisher><isbn>EPA/100/R-12/001</isbn><label>1239433</label><urls><related-urls><url>https://www.epa.gov/risk/benchmark-dose-technical-guidance</url></related-urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>]. The BMR is a predetermined change in the response rate of an adverse effect. It serves as the basis for obtaining the benchmark dose lower confidence limit (BMDL), which is the 95% lower bound of the BMD. BMRs were identified and applied consistent with quantal and continuous data and, when possible, informed by understanding of biological significance.
- **Step 4: BMD model the data.** This step involved fitting a statistical model to the dose-response data that describes the data set of the identified adverse effect. Typically, this involved selecting a family or families of models (e.g., polynomial continuous, Hill continuous, or exponential continuous) for further consideration based on the data and experimental design. In this step, a BMDL was derived by placing confidence limits (one- or two-sided) and a confidence level (typically 95%) on a BMD to obtain the dose that ensures with high confidence that the BMR is not exceeded.
- **Step 5: Determine a POD (HED).** If modeling was feasible, the estimated BMDL (HED)s were used as PODs (i.e., POD [HED]). If dose-response modeling was not feasible, NOAEL (HED)s or lowest-observed-adverse-effect level (LOAEL) (HED)s were identified.
- **Step 6: Provide rationale for selecting uncertainty factors.** Uncertainty factors were selected in accordance with U.S. EPA guidelines considering variations in sensitivity among humans, differences between animals and humans, the duration of exposure in the key study compared to a lifetime of the species studied, and the potential limitations of the toxicology database.
- **Step 7: Calculate the subchronic and chronic RfDs.** The RfDs were calculated by dividing a POD (HED) by the selected uncertainty factors.

$$\text{RfD} = \frac{\text{POD (HED)}}{\text{UF}_C}$$

where:

POD (HED) is calculated from the BMDL or NOAEL using a $BW^{3/4}$ allometric scaling approach consistent with U.S. EPA guidance [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2011</Year><RecNum>1311</RecNum><IDText>752972</IDT ext><DisplayText>(U.S. EPA, 2011b)</DisplayText><record><rec-number>1311</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1311</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Recommended use of body weight 3/4 as the default method in derivation of the oral reference dose</title></titles><pages>1-50</pages><dates><year>2011</year></dates><pub-location>Washington, DC</pub-location><publisher>U.S. Environmental Protection Agency, Risk Assessment Forum, Office of the Science Advisor</publisher><isbn>EPA/100/R-11/0001</isbn><label>752972</label><urls><related-urls><url>https://www.epa.gov/sites/production/files/2013-09/documents/recommended-use-of-bw34.pdf</url></related-urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>]

UF_C is established in accordance with U.S. EPA guidelines considering variations in sensitivity among humans, differences between animals and humans, the duration of exposure in the key study compared to a lifetime of the species studied, and the potential limitations of the toxicology database.

- **Step 8: Assignment of Confidence Levels.** In assessments in which an RfD or RfC is derived, characterization of the level of confidence in the principal study(ies), the database associated with that reference value, and the overall confidence in the reference value(s) are provided. Details on characterizing confidence are provided in Chapter 4 (specifically Section 4.3.9.2) of the U.S. EPA's *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>1994</Year><RecNum>661</RecNum><IDText>6488</IDText><DisplayText>(U.S. EPA, 1994)</DisplayText><record><rec-number>661</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604955631">661</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry</title></titles><dates><year>1994</year></dates><pub-location>Research Triangle Park, NC</pub-location><publisher>U.S. Environmental Protection Agency, Office of Research and Development, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office</publisher><isbn>EPA/600/8-90/066F</isbn><label>6488</label><work-type>EPA Report</work-type><urls><related-urls><url>https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=71993&CFID=51

174829&CFTOKEN=25006317</url></related-urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>]. For example, the ranking of confidence in the database (low, medium, or high) reflects EPA's assessment of the degree to which the reference value (e.g., RfD) might potentially change (in either direction) with the acquisition of new data.

3.0 OVERVIEW OF EVIDENCE IDENTIFICATION FOR SYNTHESIS AND DOSE-RESPONSE ANALYSIS

3.1 LITERATURE SEARCH AND SCREENING RESULTS

The database searches yielded 435 unique records, with 50 records identified from additional sources, such as TSCA submissions, posted NTP study tables, peer-review recommendations, and review of reference lists from other authoritative sources. Of the 434 studies identified, 317 were excluded during title and abstract screening, 117 were reviewed at the full-text level, and 42 were considered relevant to the PECO eligibility criteria (see [REF _Ref55814542 \h]). This included 19 epidemiologic studies (described in 22 publications), 10 in vivo animal studies (described in 15 peer-reviewed and non-peer-reviewed publications), and 5 in vitro genotoxicity studies. The detailed search approach, including the query strings and PECO criteria, is provided in Appendix A and Appendix B, respectively.

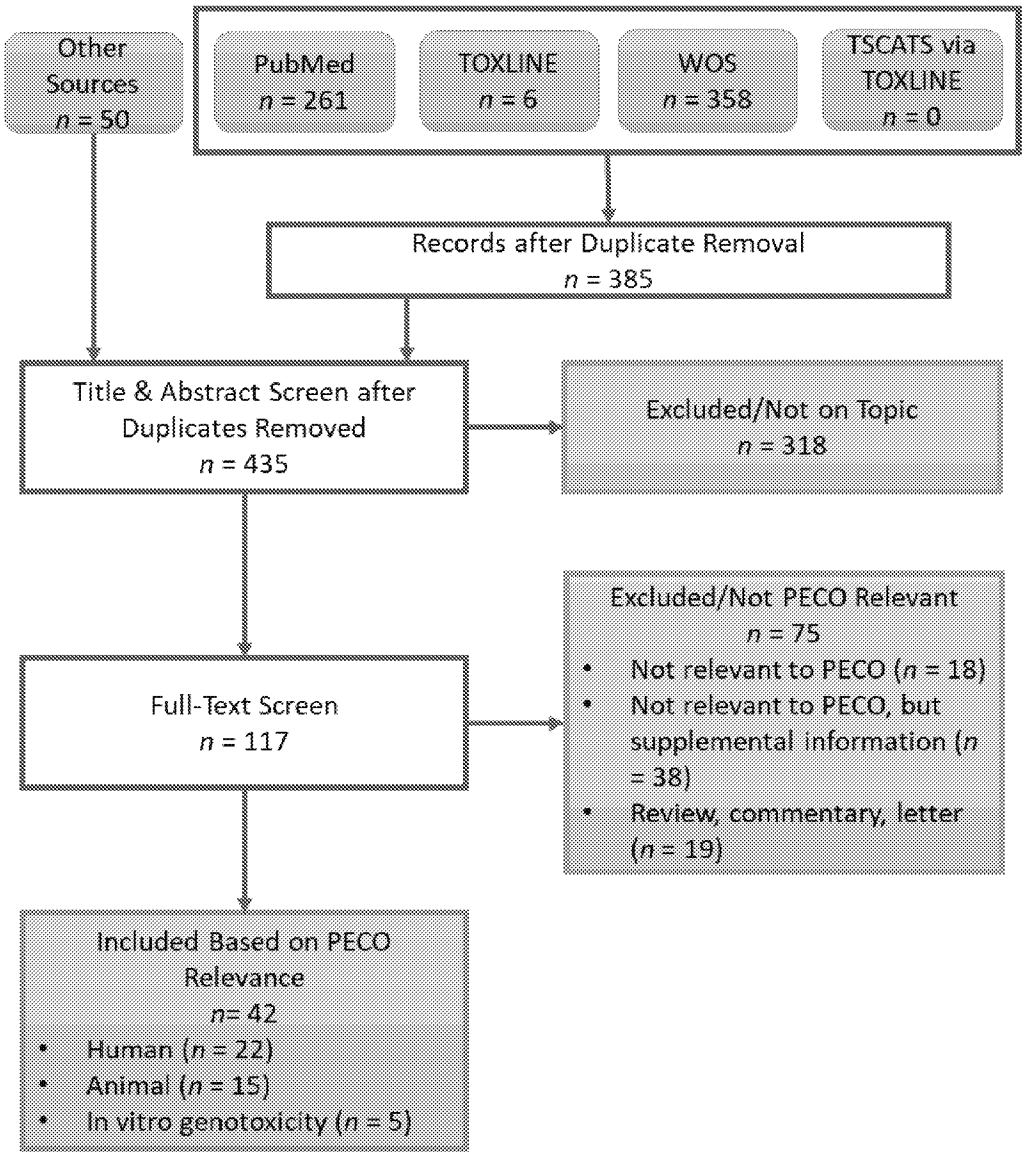

Figure [SEQ Figure * ARABIC]. Literature Search and Screening Flow Diagram for PFBS (CASRN 375-73-5)

3.2 STUDY EVALUATION RESULTS

Based on the study evaluations, seven human epidemiology studies were considered uninformative and are not discussed any further in this assessment (see [REF _Ref55818044 \h]). All animal studies were considered informative and thus were identified as relevant during literature screening and included in the evidence synthesis and dose-response analysis. Overall, 12 epidemiologic studies (described in 15 publications) and 10 in vivo animal studies (described in 15 peer-reviewed and non-peer-reviewed publications) were included in the evidence synthesis and further evaluated for use in the development of toxicity values for PFBS. As shown in Figures 5 and 6, while the database of studies on PFBS is not large, several high- and medium-confidence oral exposure studies in animals were identified, as were several

medium-confidence studies in humans. Multiple publications of the same study are not listed as independent studies in HAWC, they are reviewed together in one entry. In addition, [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3469215"] was not evaluated because the outcome (i.e., sleep disturbances) was considered a nonspecific effect, and thus was not entered into HAWC. No studies were identified evaluating the toxicity of PFBS or K^+PFBS following inhalation exposure or on the carcinogenicity of PFBS or K^+PFBS in humans or animals.

Table [SEQ Table * ARABIC]. Epidemiological Studies Excluded Based on Study Evaluation

Reference	Outcome	Reason for Exclusion
[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3860099"]	Blood pressure	Extremely poor sensitivity (96% of participants below the LOD for PFBS measurement) with no observed association.
[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=2713574"]	Depression	Serious concerns with temporality between exposure and outcome, confounding, and analysis.
[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=4238300"]	Birth size, weight gain	Extremely poor sensitivity (median exposure = 0.01 ng/g, IQR LOD-0.04, 43% below the LOD for PFBS measurement) with no observed association.
[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3351917"]	Congenital hypothyroidism	Excluded from full statistical analysis by study authors because of a high percentage below the LOD (72%) for PFBS measurement.
[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=4238334"]	Cholesterol, uric acid, diabetes, BMI, thyroid hormones	No consideration of potential confounding.
[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3469215"][a]	Sleep disturbances	Not evaluated because of nonspecific effect.
[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856459"]	Endometriosis-related infertility	Exposure measured concurrent with outcome for chronic outcome; serious concerns for exposure and outcome misclassification.

Table [SEQ Table * ARABIC]. Epidemiological Studies Excluded Based on Study Evaluation		
Reference	**Outcome**	**Reason for Exclusion**

[a][HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3469215"]was not evaluated because the outcome was sleep disturbances, which was considered a nonspecific effect, and thus was not entered in HAWC.

BMI = body mass index; HAWC = Health Assessment Workspace Collaborative; IQR = interquartile range; LOD = limit of detection; PFBS = perfluorobutane sulfonic acid.

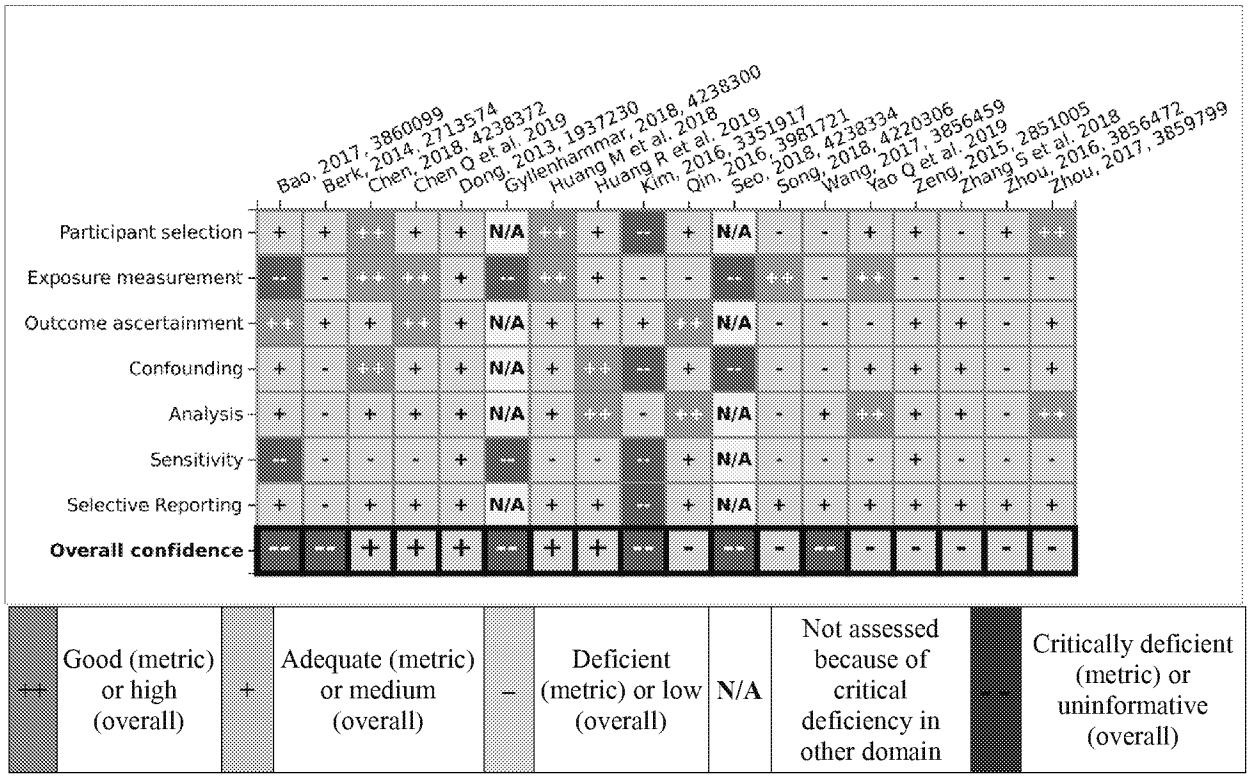

Figure [SEQ Figure * ARABIC]. Evaluation Results for Epidemiological Studies Assessing Effects of PFBS
(Click to see [HYPERLINK "https://hawcprd.epa.gov/summary/visual/100000050/"] for rating rationales)

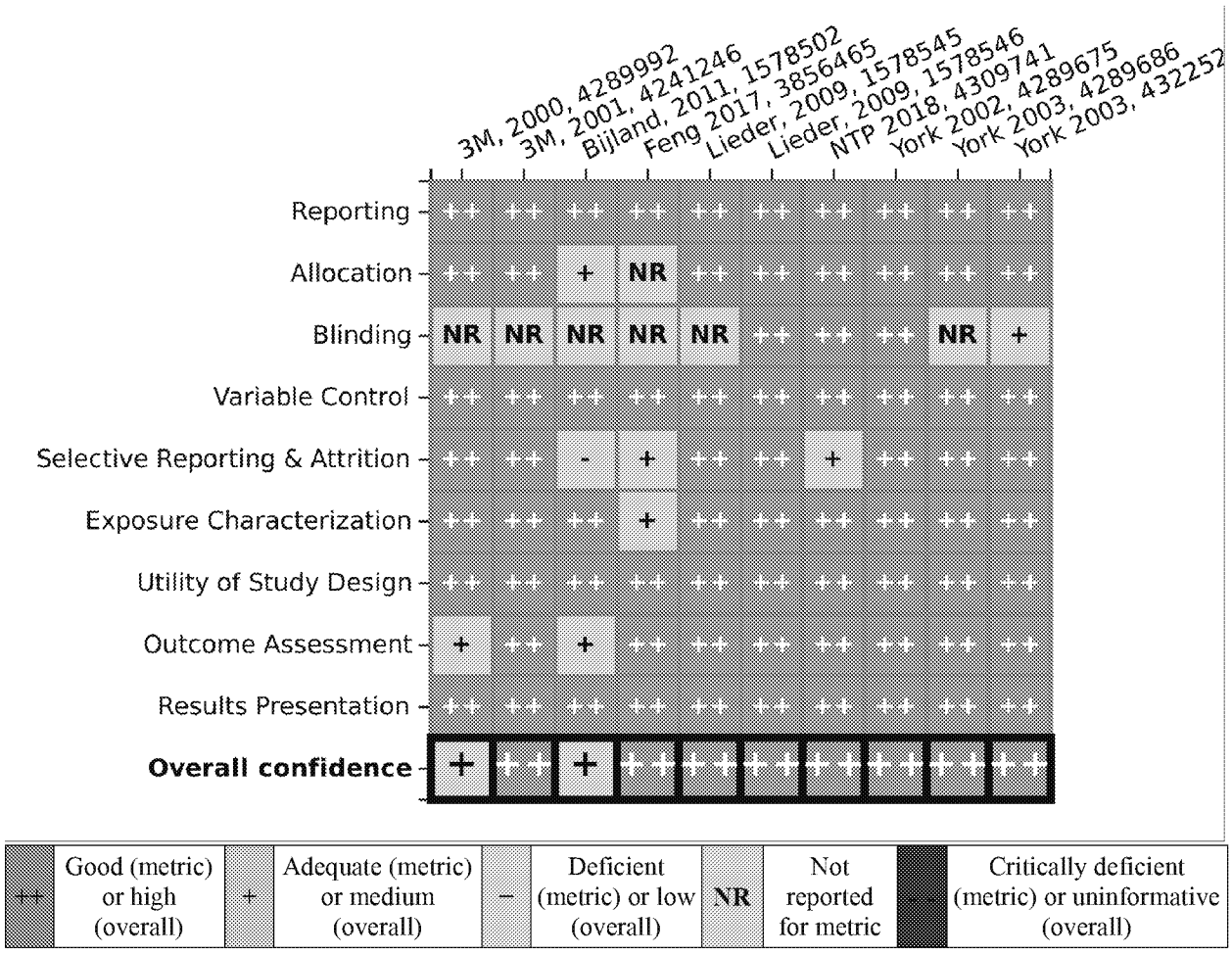

Figure [SEQ Figure * ARABIC]. Evaluation Results for Animal Studies Assessing Effects of PFBS Exposure
(Click to see [HYPERLINK "https://hawcprd.epa.gov/summary/visual/100000034/"] for rating rationales)

4.0 EVIDENCE SYNTHESIS: OVERVIEW OF INCLUDED STUDIES

The database of all repeated-dose oral toxicity studies for PFBS and the related compound K^+PFBS that are potentially relevant for deriving RfD values includes a short-term range-finding study in rats [ADDIN EN.CITE <EndNote><Cite><Author>3M</Author><Year>2000</Year><RecNum>1257</RecNum><IDText>4289992</IDText><DisplayText>(3M, 2000d)</DisplayText><record><rec-number>1257</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1257</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>3M,</author></authors></contributors><titles><title>A repeated dose range-finding toxicity study of T-7485 in Sprague-Dawley rats</title></titles><dates><year>2000</year></dates><pub-location>St. Paul, MN</pub-location><publisher>3M Pharmaceuticals</publisher><isbn>Study Number: 132-006</isbn><label>4289992</label><urls></urls><language>English</language><modified-date>3M Company</modified-date></record></Cite></EndNote>], two 28-day studies in rats [ADDIN EN.CITE <EndNote><Cite><Author>3M</Author><Year>2001</Year><RecNum>602</RecNum><IDText>4241246</IDText><DisplayText>(NTP, 2019; 3M, 2001)</DisplayText><record><rec-number>602</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604955602">602</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>3M,</author></authors></contributors><titles><title>A 28-day oral (gavage) toxicity study of T-7485 in Sprague-Dawley rats</title></titles><dates><year>2001</year></dates><pub-location>St. Paul, MN</pub-location><publisher>3M Corporate Toxicology</publisher><isbn>Study Number: 132-007</isbn><label>4241246</label><urls></urls><language>English</language><modified-date>3M Company</modified-date></record></Cite><Cite><Author>NTP</Author><Year>2019</Year><RecNum>1223</RecNum><IDText>5400978</IDText><record><rec-number>1223</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1223</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NTP,</author></authors></contributors><titles><title>NTP technical report on the toxicity studies of perfluoroalkyl sulfonates (perfluorobutane sulfonic acid, perfluorohexane sulfonate potassium salt, and perfluorooctane sulfonic acid) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats</title></titles><dates><year>2019</year></dates><pub-location>Research Triangle Park, NC</pub-location><isbn>Toxicity Report 96</isbn><label>5400978</label><urls><related-urls><url>https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox096_508.pdf</url></related-urls></urls><language>English</language><modified-date>National Toxicology Program</modified-date></record></Cite></EndNote>], one subchronic study in rats [ADDIN EN.CITE ADDIN EN.CITE.DATA], one subchronic-duration lipoprotein metabolism study in mice [ADDIN EN.CITE ADDIN EN.CITE.DATA], three gestational exposure studies in mice and rats [ADDIN EN.CITE ADDIN EN.CITE.DATA], and a two-generation reproductive toxicity study in rats [ADDIN EN.CITE ADDIN EN.CITE.DATA]. In

addition, 19 epidemiological studies (described in 22 publications) were identified that report on the association between PFBS and human health effects. Specific study limitations identified during evaluation (see HAWC) are discussed only for studies interpreted as low confidence or if a limitation affected a specific inference for drawing conclusions.

Human and animal studies have evaluated potential effects on the thyroid, reproductive systems, development, kidneys, liver, and lipid and lipoprotein homeostasis following exposure to PFBS. The evidence base for these outcomes is presented in this section. For each potential health effect, the synthesis describes the database of human and animal studies, as well as an array of the animal results across studies. NOAELs and LOAELs presented in the figures and text are based on statistical significance and/or biological significance (e.g., directionality of effect [statistically significantly decreased cholesterol/triglycerides is of unclear toxicological relevance], abnormal or irregular dose-response relationship [nonmonotonicity], tissue-specific considerations for magnitude of effect [statistically nonsignificant increase of ≥10% in liver weight interpreted as biologically significant]). A summary of the available database is presented in [REF _Ref55818122 \h] of Section 5. For information in this section, evidence to inform organ/system-specific effects of PFBS in animals following developmental exposure is discussed in the individual organ/system-specific sections (e.g., reproductive cycling endpoints after developmental exposure are discussed in the "Reproductive Effects" section). Other effects informing potential developmental effects (e.g., pup BW) are discussed in the "Offspring Growth and Early Development" section.

Evidence integration analyses and overall judgments on the hazard support for each outcome domain provided by the available human and animal studies are discussed in the "Evidence Integration and Hazard Characterization" section. Notably, in that section, the evidence informing organ/system-specific endpoints after developmental exposure was considered potentially informative to both the developmental effects outcome domain and the organ/system-specific outcome domain.

4.1 THYROID EFFECTS

4.1.1 Human Studies

One [HYPERLINK "https://hawcprd.epa.gov/rob/study/100515513/"] study examined cross-sectional associations between PFBS exposure and thyroid hormones in women with premature ovarian insufficiency [ADDIN EN.CITE <EndNote><Cite><Author>Zhang</Author><Year>2018</Year><RecNum>447</RecNum><IDText>5079665</IDText><DisplayText>(Zhang et al., 2018)</DisplayText><record><rec-number>447</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604955527">447</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zhang, S.</author><author>Tan, R.</author><author>Pan, R.</author><author>Xiong, J.</author><author>Tian, Y.</author><author>Wu, J.</author><author>Chen, L.</author></authors></contributors><titles><title>Association of perfluoroalkyl and polyfluoroalkyl substances with premature ovarian insufficiency in Chinese women</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title><alt-title>J Clin Endocrinol Metab</alt-title><short-title>Journal of Clinical Endocrinology and Metabolism</short-title></titles><periodical><full-title>Journal of Clinical Endocrinology

and Metabolism</full-title><abbr-1>J Clin Endocrinol Metab</abbr-1></periodical><alt-periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title><abbr-1>J Clin Endocrinol Metab</abbr-1></alt-periodical><pages>2543-2551</pages><volume>103</volume><number>7</number><dates><year>2018</year></dates><isbn>ISSN 0021-972X
EISSN 1945-7197</isbn><accession-num>29986037</accession-num><label>5079665</label><urls><related-urls><url>http://dx.doi.org/10.1210/jc.2017-02783</url></related-urls></urls><electronic-resource-num>10.1210/jc.2017-02783</electronic-resource-num><language>English</language></record></Cite></EndNote>] and reported no association with free T_3, free T_4, or thyroid-stimulating hormone. However, this study had poor sensitivity and methodological limitations that make interpreting these null results difficult; further, the results in this highly selected population may not be generalizable.

4.1.2 Animal Studies

Two high-confidence studies evaluated the effects of PFBS exposure on the thyroid, specifically thyroid hormone levels, thyroid histopathology, and thyroid weight [ADDIN EN.CITE ADDIN EN.CITE.DATA] (see [REF _Ref55814607 \h]). Dams exposed to K^+PFBS through gestation (GDs 1–20) exhibited a statistically significant decrease in [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-t3-effect-size-animal/"], [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-t4-effect-size-animal/"] and [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-t4-effect-size-animal/"] (reduced 17, 21, and 12%, respectively, relative to control at 200 mg/kg-day and reduced 16, 20, and 11%, respectively, relative to control at 500 mg/kg-day) on GD 20 at doses of 200 and 500 mg/kg-day, but not at 50 mg/kg-day [ADDIN EN.CITE <EndNote><Cite><Author>Feng</Author><Year>2017</Year><RecNum>1031</RecNum><IDText>3856465</IDText><DisplayText>(Feng et al., 2017)</DisplayText><record><rec-number>1031</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1031</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Feng, X.</author><author>Cao, X.</author><author>Zhao, S.</author><author>Wang, X.</author><author>Hua, X.</author><author>Chen, L.</author><author>Chen, L.</author></authors></contributors><titles><title>Exposure of pregnant mice to perfluorobutanesulfonate causes hypothyroxinemia and developmental abnormalities in female offspring</title><secondary-title>Toxicological Sciences</secondary-title><alt-title>Toxicol Sci</alt-title><short-title>Toxicological Sciences</short-title></titles><periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></periodical><alt-periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></alt-periodical><pages>409-419</pages><volume>155</volume><number>2</number><dates><year>2017</year></dates><isbn>ISSN 1096-6080
EISSN 1096-0929</isbn><accession-num>27803384</accession-num><label>3856465</label><urls><related-urls><url>http://dx.doi.org/10.1093/toxsci/kfw219</url></related-urls></urls><electronic-resource-num>10.1093/toxsci/kfw219</electronic-resource-num><language>English</language></record></Cite></EndNote>]. Decreased [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-t3-effect-size-

animal/"] and [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-t4-effect-size-animal/"] were also reported at PNDs 1, 30, and 60 in offspring gestationally exposed to K^+PFBS at the same doses (up to 37% reduction in T_3 and 52% reduction in T_4). Increased thyroid-stimulating hormone ([HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-tsh-effect-size-animal/"]) was reported in dams and pubertal (PND 30) offspring (21 and 14% relative to control at 200 mg/kg-day, respectively) exposed gestationally to K^+PFBS. Statistically significant dose-dependent decreases in [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-t3-effect-size-animal/"], [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-t4-effect-size-animal/"], and [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-t4-effect-size-animal/"] were also reported after exposure in male and female rats to K^+PFBS for 28 days at all doses tested (≥62.6 mg/kg-day) [ADDIN EN.CITE
<EndNote><Cite><Author>NTP</Author><Year>2019</Year><RecNum>1223</RecNum><IDText>5400978</IDText><DisplayText>(NTP, 2019)</DisplayText><record><rec-number>1223</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1223</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NTP,</author></authors></contributors><titles><title>NTP technical report on the toxicity studies of perfluoroalkyl sulfonates (perfluorobutane sulfonic acid, perfluorohexane sulfonate potassium salt, and perfluorooctane sulfonic acid) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats</title></titles><dates><year>2019</year></dates><pub-location>Research Triangle Park, NC</pub-location><isbn>Toxicity Report 96</isbn><label>5400978</label><urls><related-urls><url>https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox096_508.pdf</url></related-urls></urls><language>English</language><modified-date>National Toxicology Program</modified-date></record></Cite></EndNote>]. The reported reductions in rat total T_3 were up to −57% (male) and −43% (female), in free T_4 up to −86% (male) and −77% (female), and in total T_4 up to −97% (male) and −71% (female). Dose-response graphics for T_4, T_3, and TSH, including effect size and variability, are included in Appendix E, Figures [REF _Ref55819266 \h], [REF _Ref55819277 \h], and [REF _Ref55819284 \h], respectively. Thyroid gland weight, thyroid histopathology, and [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-tsh-effect-size-animal/"] were not changed after 28 days of PFBS exposure in male or female rats at doses up to 1,000 mg/kg-day [ADDIN EN.CITE
<EndNote><Cite><Author>NTP</Author><Year>2019</Year><RecNum>1223</RecNum><IDText>5400978</IDText><DisplayText>(NTP, 2019)</DisplayText><record><rec-number>1223</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1223</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NTP,</author></authors></contributors><titles><title>NTP technical report on the toxicity studies of perfluoroalkyl sulfonates (perfluorobutane sulfonic acid, perfluorohexane sulfonate potassium salt, and perfluorooctane sulfonic acid) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats</title></titles><dates><year>2019</year></dates><pub-location>Research Triangle Park,

NC</pub-location><isbn>Toxicity Report 96</isbn><label>5400978</label><urls><related-urls><url>https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox096_508.pdf</url></related-urls></urls><language>English</language><modified-date>National Toxicology Program</modified-date></record></Cite></EndNote>].

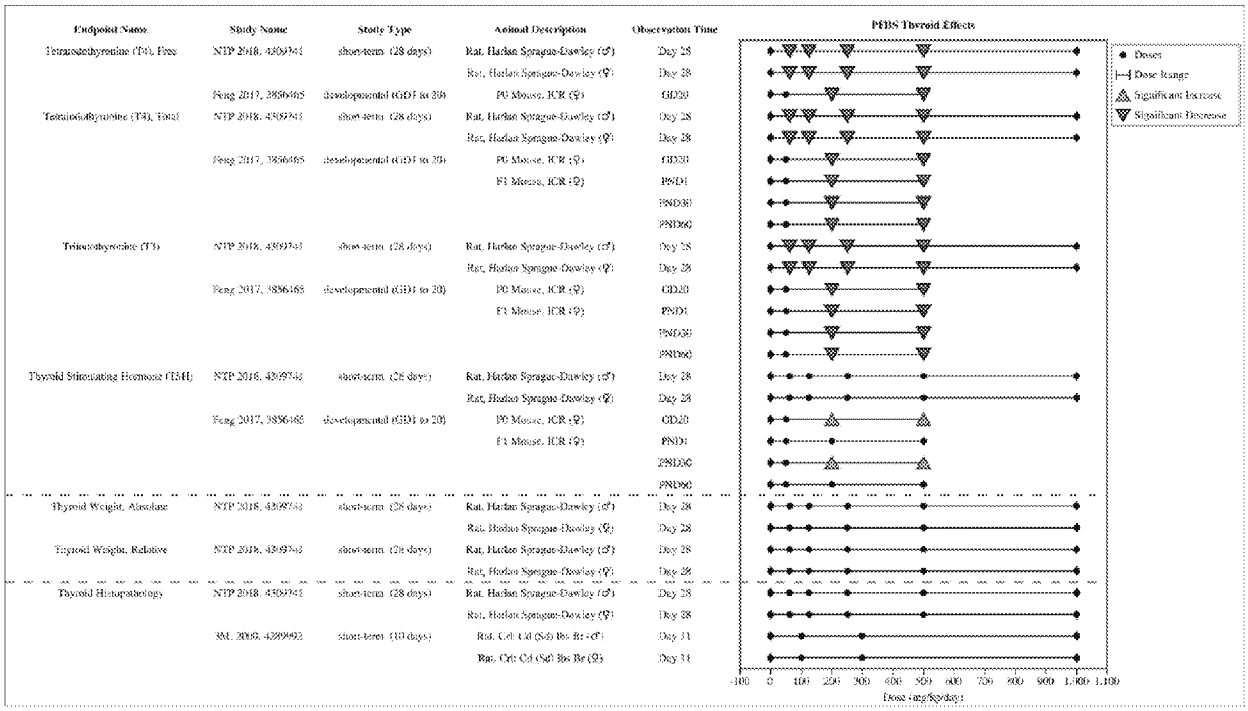

Figure [SEQ Figure * ARABIC]. Thyroid Effects from K^+PFBS Exposure (Click to see interactive data graphic and rationale for study evaluations for [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-thyroid-effects/"] in HAWC)

4.2 REPRODUCTIVE EFFECTS

4.2.1 Human Studies

Five studies of populations in China and Taiwan examined different reproductive outcomes in women and men [ADDIN EN.CITE ADDIN EN.CITE.DATA].

Three [HYPERLINK "https://hawcprd.epa.gov/rob/study/100000898/"] studies examined reproductive hormones in newborn boys and girls in China [ADDIN EN.CITE <EndNote><Cite><Author>Yao</Author><Year>2019</Year><RecNum>947</RecNum><DisplayText>(Yao et al., 2019)</DisplayText><record><rec-number>947</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">947</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Yao, Q.</author><author>Shi, R.</author><author>Wang, C.</author><author>Han, W.</author><author>Gao, Y.</author><author>Zhang, Y.</author><author>Zhou, Y.</author><author>Ding,

G.</author><author>Tian, Y.</author></authors></contributors><titles><title>Cord blood per- and polyfluoroalkyl substances, placental steroidogenic enzyme, and cord blood reproductive hormone</title><secondary-title>Environment International</secondary-title><alt-title>Environ Int</alt-title><short-title>Environment International</short-title></titles><periodical><full-title>Environment International</full-title><abbr-1>Environ Int</abbr-1></periodical><alt-periodical><full-title>Environment International</full-title><abbr-1>Environ Int</abbr-1></alt-periodical><pages>573-582</pages><volume>129</volume><number>Elsevier</number><dates><year>2019</year></dates><isbn>ISSN 0160-4120
EISSN 1873-6750</isbn><accession-num>31174145</accession-num><label>5187556</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.envint.2019.03.047</url></related-urls></urls><electronic-resource-num>10.1016/j.envint.2019.03.047</electronic-resource-num><language>English</language></record></Cite></EndNote>], adolescent boys and girls in Taiwan [ADDIN EN.CITE <EndNote><Cite><Author>Zhou</Author><Year>2016</Year><RecNum>956</RecNum><IDText>3856472</IDText><DisplayText>(Zhou et al., 2016)</DisplayText><record><rec-number>956</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">956</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zhou, Y.</author><author>Hu, L. W.</author><author>Qian, Z. M.</author><author>Chang, J. J.</author><author>King, C.</author><author>Paul, G.</author><author>Lin, S.</author><author>Chen, P. C.</author><author>Lee, Y. L.</author><author>Dong, G. H.</author></authors></contributors><titles><title>Association of perfluoroalkyl substances exposure with reproductive hormone levels in adolescents: By sex status</title><secondary-title>Environment International</secondary-title><alt-title>Environ Int</alt-title><short-title>Environment International</short-title></titles><periodical><full-title>Environment International</full-title><abbr-1>Environ Int</abbr-1></periodical><alt-periodical><full-title>Environment International</full-title><abbr-1>Environ Int</abbr-1></alt-periodical><pages>189-195</pages><volume>94</volume><number>Elsevier</number><dates><year>2016</year></dates><isbn>ISSN 0160-4120
EISSN 1873-6750</isbn><accession-num>27258660</accession-num><label>3856472</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.envint.2016.05.018</url></related-urls></urls><electronic-resource-num>10.1016/j.envint.2016.05.018</electronic-resource-num><language>English</language></record></Cite></EndNote>], and adult women in China [ADDIN EN.CITE <EndNote><Cite><Author>Zhang</Author><Year>2018</Year><RecNum>447</RecNum><IDText>5079665</IDText><DisplayText>(Zhang et al., 2018)</DisplayText><record><rec-number>447</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604955527">447</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zhang, S.</author><author>Tan, R.</author><author>Pan, R.</author><author>Xiong, J.</author><author>Tian, Y.</author><author>Wu, J.</author><author>Chen, L.</author></authors></contributors><titles><title>Association of perfluoroalkyl and polyfluoroalkyl substances with premature ovarian insufficiency in Chinese women</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-

title><alt-title>J Clin Endocrinol Metab</alt-title><short-title>Journal of Clinical Endocrinology and Metabolism</short-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title><abbr-1>J Clin Endocrinol Metab</abbr-1></periodical><alt-periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title><abbr-1>J Clin Endocrinol Metab</abbr-1></alt-periodical><pages>2543-2551</pages><volume>103</volume><number>7</number><dates><year>2018</year></dates><isbn>ISSN 0021-972X
EISSN 1945-7197</isbn><accession-num>29986037</accession-num><label>5079665</label><urls><related-urls><url>http://dx.doi.org/10.1210/jc.2017-02783</url></related-urls></urls><electronic-resource-num>10.1210/jc.2017-02783</electronic-resource-num><language>English</language></record></Cite></EndNote>]. The study in newborns reported lower testosterone (β: −0.23; 95% CI: −0.46−0.01) and estradiol (β: −0.09; 95% CI: −0.2−0.01) in cord blood in male babies, but these differences were not statistically significant [ADDIN EN.CITE <EndNote><Cite><Author>Yao</Author><Year>2019</Year><RecNum>947</RecNum><DisplayText>(Yao et al., 2019)</DisplayText><record><rec-number>947</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">947</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Yao, Q.</author><author>Shi, R.</author><author>Wang, C.</author><author>Han, W.</author><author>Gao, Y.</author><author>Zhang, Y.</author><author>Zhou, Y.</author><author>Ding, G.</author><author>Tian, Y.</author></authors></contributors><titles><title>Cord blood per- and polyfluoroalkyl substances, placental steroidogenic enzyme, and cord blood reproductive hormone</title><secondary-title>Environment International</secondary-title><alt-title>Environ Int</alt-title><short-title>Environment International</short-title></titles><periodical><full-title>Environment International</full-title><abbr-1>Environ Int</abbr-1></periodical><alt-periodical><full-title>Environment International</full-title><abbr-1>Environ Int</abbr-1></alt-periodical><pages>573-582</pages><volume>129</volume><number>Elsevier</number><dates><year>2019</year></dates><isbn>ISSN 0160-4120
EISSN 1873-6750</isbn><accession-num>31174145</accession-num><label>5187556</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.envint.2019.03.047</url></related-urls></urls><electronic-resource-num>10.1016/j.envint.2019.03.047</electronic-resource-num><language>English</language></record></Cite></EndNote>]. The other two studies reported no clear associations between PFBS levels and reproductive hormones in women with premature ovarian insufficiency [ADDIN EN.CITE <EndNote><Cite><Author>Zhang</Author><Year>2018</Year><RecNum>447</RecNum><IDText>5079665</IDText><DisplayText>(Zhang et al., 2018)</DisplayText><record><rec-number>447</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604955527">447</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zhang, S.</author><author>Tan, R.</author><author>Pan, R.</author><author>Xiong, J.</author><author>Tian, Y.</author><author>Wu, J.</author><author>Chen, L.</author></authors></contributors><titles><title>Association of perfluoroalkyl and polyfluoroalkyl substances with premature ovarian insufficiency in Chinese women</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-

title><alt-title>J Clin Endocrinol Metab</alt-title><short-title>Journal of Clinical Endocrinology and Metabolism</short-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title><abbr-1>J Clin Endocrinol Metab</abbr-1></periodical><alt-periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title><abbr-1>J Clin Endocrinol Metab</abbr-1></alt-periodical><pages>2543-2551</pages><volume>103</volume><number>7</number><dates><year>2018</year></dates><isbn>ISSN 0021-972X
EISSN 1945-7197</isbn><accession-num>29986037</accession-num><label>5079665</label><urls><related-urls><url>http://dx.doi.org/10.1210/jc.2017-02783</url></related-urls></urls><electronic-resource-num>10.1210/jc.2017-02783</electronic-resource-num><language>English</language></record></Cite></EndNote>] or in adolescents, either among the entire study population or stratified by sex [ADDIN EN.CITE <EndNote><Cite><Author>Zhou</Author><Year>2016</Year><RecNum>956</RecNum><IDText>3856472</IDText><DisplayText>(Zhou et al., 2016)</DisplayText><record><rec-number>956</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">956</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zhou, Y.</author><author>Hu, L. W.</author><author>Qian, Z. M.</author><author>Chang, J. J.</author><author>King, C.</author><author>Paul, G.</author><author>Lin, S.</author><author>Chen, P. C.</author><author>Lee, Y. L.</author><author>Dong, G. H.</author></authors></contributors><titles><title>Association of perfluoroalkyl substances exposure with reproductive hormone levels in adolescents: By sex status</title><secondary-title>Environment International</secondary-title><alt-title>Environ Int</alt-title><short-title>Environment International</short-title></titles><periodical><full-title>Environment International</full-title><abbr-1>Environ Int</abbr-1></periodical><alt-periodical><full-title>Environment International</full-title><abbr-1>Environ Int</abbr-1></alt-periodical><pages>189-195</pages><volume>94</volume><number>Elsevier</number><dates><year>2016</year></dates><isbn>ISSN 0160-4120
EISSN 1873-6750</isbn><accession-num>27258660</accession-num><label>3856472</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.envint.2016.05.018</url></related-urls></urls><electronic-resource-num>10.1016/j.envint.2016.05.018</electronic-resource-num><language>English</language></record></Cite></EndNote>].

One [HYPERLINK "https://hawcprd.epa.gov/rob/study/100001467/"] cross-sectional study [ADDIN EN.CITE <EndNote><Cite><Author>Song</Author><Year>2018</Year><RecNum>955</RecNum><IDText>4220306</IDText><DisplayText>(Song et al., 2018)</DisplayText><record><rec-number>955</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">955</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Song, X.</author><author>Tang, S.</author><author>Zhu, H.</author><author>Chen, Z.</author><author>Zang, Z.</author><author>Zhang, Y.</author><author>Niu, X.</author><author>Wang, X.</author><author>Yin, H.</author><author>Zeng, F.</author><author>He, C.</author></authors></contributors><titles><title>Biomonitoring PFAAs in blood and semen samples: Investigation of a potential link between PFAAs exposure

and semen mobility in China</title><secondary-title>Environment International</secondary-title><alt-title>Environ Int</alt-title><short-title>Environment International</short-title></titles><periodical><full-title>Environment International</full-title><abbr-1>Environ Int</abbr-1></periodical><alt-periodical><full-title>Environment International</full-title><abbr-1>Environ Int</abbr-1></alt-periodical><pages>50-54</pages><volume>113</volume><number>Elsevier</number><dates><year>2018</year></dates><isbn>ISSN 0160-4120
EISSN 1873-6750</isbn><accession-num>29421407</accession-num><label>4220306</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.envint.2018.01.010</url></related-urls></urls><electronic-resource-num>10.1016/j.envint.2018.01.010</electronic-resource-num><language>English</language></record></Cite></EndNote>] examined the association between PFBS exposure and semen parameters. There was no indication of decreased semen quality in this study (correlation coefficients of −0.022 for semen concentration and 0.195 [$p < 0.05$] for progressive motility), although issues were noted regarding the ability of this study to detect an effect and important methodological details were missing.

Two studies examined other female reproductive effects: a cross-sectional study of menstrual cycle characteristics in a general population sample of women planning to become pregnant who were enrolled at preconception care clinics in China [ADDIN EN.CITE <EndNote><Cite><Author>Zhou</Author><Year>2017</Year><RecNum>831</RecNum><DisplayText>(Zhou et al., 2017a)</DisplayText><record><rec-number>831</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">831</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zhou, W.</author><author>Zhang, L.</author><author>Tong, C.</author><author>Fang, F.</author><author>Zhao, S.</author><author>Tian, Y.</author><author>Tao, Y.</author><author>Zhang, J.</author></authors></contributors><titles><title>Plasma perfluoroalkyl and polyfluoroalkyl substances concentration and menstrual cycle characteristics in preconception women</title><secondary-title>Environmental Health Perspectives</secondary-title><alt-title>Environ Health Perspect</alt-title><short-title>Environmental Health Perspectives</short-title></titles><periodical><full-title>Environmental Health Perspectives</full-title><abbr-1>Environ Health Perspect</abbr-1></periodical><alt-periodical><full-title>Environmental Health Perspectives</full-title><abbr-1>Environ Health Perspect</abbr-1></alt-periodical><pages>067012</pages><volume>125</volume><number>6</number><dates><year>2017</year></dates><isbn>ISSN 0091-6765
EISSN 1552-9924</isbn><accession-num>28657892</accession-num><label>3859799</label><urls><related-urls><url>http://dx.doi.org/10.1289/EHP1203</url></related-urls></urls><electronic-resource-num>10.1289/ehp1203</electronic-resource-num><language>English</language></record></Cite></EndNote>] and a case-control study in China of premature ovarian insufficiency [ADDIN EN.CITE <EndNote><Cite><Author>Zhang</Author><Year>2018</Year><RecNum>447</RecNum><IDText>5079665</IDText><DisplayText>(Zhang et al., 2018)</DisplayText><record><rec-number>447</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604955527">447</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zhang, S.</author><author>Tan, R.</author><author>Pan, R.</author><author>Xiong,

J.</author><author>Tian, Y.</author><author>Wu, J.</author><author>Chen, L.</author></authors></contributors><titles><title>Association of perfluoroalkyl and polyfluoroalkyl substances with premature ovarian insufficiency in Chinese women</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title><alt-title>J Clin Endocrinol Metab</alt-title><short-title>Journal of Clinical Endocrinology and Metabolism</short-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title><abbr-1>J Clin Endocrinol Metab</abbr-1></periodical><alt-periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title><abbr-1>J Clin Endocrinol Metab</abbr-1></alt-periodical><pages>2543-2551</pages><volume>103</volume><number>7</number><dates><year>2018</year></dates><isbn>ISSN 0021-972X
EISSN 1945-7197</isbn><accession-num>29986037</accession-num><label>5079665</label><urls><related-urls><url>http://dx.doi.org/10.1210/jc.2017-02783</url></related-urls></urls><electronic-resource-num>10.1210/jc.2017-02783</electronic-resource-num><language>English</language></record></Cite></EndNote>], defined by FSH level and oligo/amenorrhea. For any outcome related to menstruation, there is significant potential for reverse causation because menstruation is a potential mechanism by which PFAS are removed from the body [ADDIN EN.CITE ADDIN EN.CITE.DATA]; therefore, both of these studies are considered low confidence. [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3859799"] reported adjusted odds ratios (OR) of 1.30 (95% CI: 0.54−3.12) for menorrhagia and 1.48 (95% CI: 0.54−4.03) for hypomenorrhea in preconception women in China for each one unit increase in PFBS, but these results were not statistically significant. The study authors also reported inverse statistically nonsignificant associations for these two outcomes based on exposure quartiles (OR range: 0.61−0.84 for the highest quartiles relative to the referent) with no evidence of an exposure-response relationship, indicating that the associations are not robust. All of the analyses in this study examined continuous outcome measures. [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5079665"] reported no increase in odds of premature ovarian insufficiency with higher PFBS exposure (OR for tertile 2 vs. tertile 1: 0.84, 95% CI: 0.44–1.60; OR for tertile 3: 0.92, 95% CI: 0.48–1.76).

4.2.2 Animal Studies

Reproductive outcomes were evaluated in a high-confidence study of prenatal exposure to PFBS in mice [ADDIN EN.CITE <EndNote><Cite><Author>Feng</Author><Year>2017</Year><RecNum>1031</RecNum><IDText>3856465</IDText><DisplayText>(Feng et al., 2017)</DisplayText><record><rec-number>1031</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1031</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Feng, X.</author><author>Cao, X.</author><author>Zhao, S.</author><author>Wang, X.</author><author>Hua, X.</author><author>Chen, L.</author><author>Chen, L.</author></authors></contributors><titles><title>Exposure of pregnant mice to perfluorobutanesulfonate causes hypothyroxinemia and developmental abnormalities in female offspring</title><secondary-title>Toxicological Sciences</secondary-title><alt-title>Toxicol Sci</alt-title><short-title>Toxicological Sciences</short-title></titles><periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></periodical><alt-

periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></alt-periodical><pages>409-419</pages><volume>155</volume><number>2</number><dates><year>2017</year></dates><isbn>ISSN 1096-6080
EISSN 1096-0929</isbn><accession-num>27803384</accession-num><label>3856465</label><urls><related-urls><url>http://dx.doi.org/10.1093/toxsci/kfw219</url></related-urls></urls><electronic-resource-num>10.1093/toxsci/kfw219</electronic-resource-num><language>English</language></record></Cite></EndNote>], in two high-confidence gestational exposure studies in rats [ADDIN EN.CITE <EndNote><Cite><Author>York</Author><Year>2002</Year><RecNum>1261</RecNum><IDText>4289675</IDText><DisplayText>(York, 2003c, 2002)</DisplayText><record><rec-number>1261</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1261</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>York, R. G.</author></authors></contributors><titles><title>Oral (gavage) developmental toxicity study of potassium perfluorobutane sulfonate (PFBS) in rats</title></titles><dates><year>2002</year></dates><pub-location>St. Paul, MN</pub-location><publisher>3M Corporate Toxicology</publisher><isbn>Argus Research Protocol Number 418-023</isbn><label>4289675</label><urls></urls><language>English</language></record></Cite><Cite><Author>York</Author><Year>2003</Year><RecNum>1260</RecNum><IDText>4289686</IDText><record><rec-number>1260</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1260</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>York, R. G.</author></authors></contributors><titles><title>Oral (gavage) two-generation (one litter per generation) reproduction study of perfluorobutane sulfonate (PFBS) in rats</title></titles><dates><year>2003</year></dates><pub-location>Washington, D.C.</pub-location><publisher>U.S. Environmental Protection Agency</publisher><isbn>Argus Research Protocol Number 418-021</isbn><label>4289686</label><urls></urls><language>English</language></record></Cite></EndNote>], in high-confidence short-term and subchronic studies in rats [[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5400978"] and [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578546"], respectively], and in a high-confidence two-generation reproductive study in rats [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1044</RecNum><IDText>1578545</IDText><DisplayText>(Lieder et al., 2009b)</DisplayText><record><rec-number>1044</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1044</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lieder, P. H.</author><author>York, R. G.</author><author>Hakes, D. C.</author><author>Chang, S. C.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>A two-generation oral gavage reproduction study with potassium perfluorobutanesulfonate (K+PFBS) in Sprague Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-

title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>33-45</pages><volume>259</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>19428941</accession-num><label>1578545</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2009.01.027</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2009.01.027</electronic-resource-num><language>English</language></record></Cite></EndNote>]. Endpoints evaluated in these studies include fertility and pregnancy outcomes, hormone levels, markers of reproductive development, and reproductive organ weights.

4.2.2.1 Female Fertility and Pregnancy Outcomes

Female fertility parameters were evaluated by both [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"] and [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578545"], who reported generally no effects in exposed parents, but some effects after gestational exposure in the F_1 offspring (click to see interactive graphic for [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-female-fertility-effects/"] in HAWC). Female fertility (e.g., fertility index and days in cohabitation) and delivery parameters (e.g., length of gestation, % deliveries, stillborn pups, and implantation sites) evaluated in [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578545"] were generally unaffected by K^+PFBS treatment for P_0- and F_1-generation dams at doses up to 1,000 mg/kg-day. The mean number of live born F_1 pups was statistically significantly decreased in the 30-mg/kg-day group, but this change was not dose dependent. The viability index in F_1 pups and the lactation index in F_1 and F_2 pups showed statistically significant changes at various doses but were not dose dependent [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1044</RecNum><IDText>1578545</IDText><DisplayText>(Lieder et al., 2009b)</DisplayText><record><rec-number>1044</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1044</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lieder, P. H.</author><author>York, R. G.</author><author>Hakes, D. C.</author><author>Chang, S. C.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>A two-generation oral gavage reproduction study with potassium perfluorobutanesulfonate (K+PFBS) in Sprague Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>33-45</pages><volume>259</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>19428941</accession-num><label>1578545</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2009.01.027</url></related-urls></urls><electronic-

resource-num>10.1016/j.tox.2009.01.027</electronic-resource-num><language>English</language></record></Cite></EndNote>]. Similarly, no effects were observed in delivery and litter parameters (e.g., implantations, litter sizes, live fetuses, corpora lutea, and early resorptions) following prenatal exposure from GDs 6 to 20 [ADDIN EN.CITE <EndNote><Cite><Author>York</Author><Year>2003</Year><RecNum>1260</RecNum><IDText>4289686</IDText><DisplayText>(York, 2003c, 2002)</DisplayText><record><rec-number>1260</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1260</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>York, R. G.</author></authors></contributors><titles><title>Oral (gavage) two-generation (one litter per generation) reproduction study of perfluorobutane sulfonate (PFBS) in rats</title></titles><dates><year>2003</year></dates><pub-location>Washington, D.C.</pub-location><publisher>U.S. Environmental Protection Agency</publisher><isbn>Argus Research Protocol Number 418-021</isbn><label>4289686</label><urls></urls><language>English</language></record></Cite><Cite><Author>York</Author><Year>2002</Year><RecNum>1261</RecNum><IDText>4289675</IDText><record><rec-number>1261</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1261</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>York, R. G.</author></authors></contributors><titles><title>Oral (gavage) developmental toxicity study of potassium perfluorobutane sulfonate (PFBS) in rats</title></titles><dates><year>2002</year></dates><pub-location>St. Paul, MN</pub-location><publisher>3M Corporate Toxicology</publisher><isbn>Argus Research Protocol Number 418-023</isbn><label>4289675</label><urls></urls><language>English</language></record></Cite></EndNote>]. Adult (PND 60) F_1 females gestationally exposed to PFBS at doses ≥200 mg/kg-day, however, exhibited fewer primordial, primary, secondary, early antral, antral, and preovulatory follicles, as well as fewer corpora lutea than control animals [ADDIN EN.CITE <EndNote><Cite><Author>Feng</Author><Year>2017</Year><RecNum>1031</RecNum><IDText>3856465</IDText><DisplayText>(Feng et al., 2017)</DisplayText><record><rec-number>1031</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1031</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Feng, X.</author><author>Cao, X.</author><author>Zhao, S.</author><author>Wang, X.</author><author>Hua, X.</author><author>Chen, L.</author><author>Chen, L.</author></authors></contributors><titles><title>Exposure of pregnant mice to perfluorobutanesulfonate causes hypothyroxinemia and developmental abnormalities in female offspring</title><secondary-title>Toxicological Sciences</secondary-title><alt-title>Toxicol Sci</alt-title><short-title>Toxicological Sciences</short-title></titles><periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></periodical><alt-periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></alt-periodical><pages>409-419</pages><volume>155</volume><number>2</number><dates><year>2017</year></dates><isbn>ISSN 1096-6080
EISSN 1096-0929</isbn><accession-num>27803384</accession-num><label>3856465</label><urls><related-

urls><url>http://dx.doi.org/10.1093/toxsci/kfw219</url></related-urls></urls><electronic-resource-num>10.1093/toxsci/kfw219</electronic-resource-num><language>English</language></record></Cite></EndNote>]. Importantly, no effects on the health (e.g., weight gain) of the exposed dams were observed at any dose [ADDIN EN.CITE <EndNote><Cite><Author>Feng</Author><Year>2017</Year><RecNum>1031</RecNum><IDText>3856465</IDText><DisplayText>(Feng et al., 2017)</DisplayText><record><rec-number>1031</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1031</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Feng, X.</author><author>Cao, X.</author><author>Zhao, S.</author><author>Wang, X.</author><author>Hua, X.</author><author>Chen, L.</author><author>Chen, L.</author></authors></contributors><titles><title>Exposure of pregnant mice to perfluorobutanesulfonate causes hypothyroxinemia and developmental abnormalities in female offspring</title><secondary-title>Toxicological Sciences</secondary-title><alt-title>Toxicol Sci</alt-title><short-title>Toxicological Sciences</short-title></titles><periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></periodical><alt-periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></alt-periodical><pages>409-419</pages><volume>155</volume><number>2</number><dates><year>2017</year></dates><isbn>ISSN 1096-6080
EISSN 1096-0929</isbn><accession-num>27803384</accession-num><label>3856465</label><urls><related-urls><url>http://dx.doi.org/10.1093/toxsci/kfw219</url></related-urls></urls><electronic-resource-num>10.1093/toxsci/kfw219</electronic-resource-num><language>English</language></record></Cite></EndNote>]. [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578545"] evaluated ovarian follicles in F_1 females after they were mated and their pups had been weaned (i.e., Lactation Day [LD] 22) and observed no effects compared with controls at 1,000 mg/kg-day; however, however, no quantitative data were reported. Ovarian parameters were not evaluated in the study by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=4289675"].

4.2.2.2 Male Fertility

Two studies using S-D rats evaluated several potential responses in the male reproductive system [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Male fertility parameters and reproductive effects (e.g., sperm parameters) were generally unaffected by K^+PFBS treatment in P_0- and F_1-generation males observed by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578545"]. At the highest dose, there were statistically significant increases in the percentage of abnormal sperm in F_1 animals and decreases in testicular sperm count in P_0-generation males. In addition, the study authors reported that the number of spermatids per gram testis was within the historical control of the testing facility. These effects were not statistically changed at lower doses. Alterations in parameters such as sperm count/number and morphology are considered indicative of adverse responses in the male reproductive system [ADDIN EN.CITE ADDIN EN.CITE.DATA]. A 28-day exposure study reported a decreased trend in testicular spermatid count per mg testis evaluated at the time of necropsy; however, no significant effects on other sperm measures were reported, including caudal epididymal sperm count and sperm motility [ADDIN EN.CITE

<EndNote><Cite><Author>NTP</Author><Year>2019</Year><RecNum>1223</RecNum><IDText>5400978</IDText><DisplayText>(NTP, 2019)</DisplayText><record><rec-number>1223</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1223</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NTP,</author></authors></contributors><titles><title>NTP technical report on the toxicity studies of perfluoroalkyl sulfonates (perfluorobutane sulfonic acid, perfluorohexane sulfonate potassium salt, and perfluorooctane sulfonic acid) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats</title></titles><dates><year>2019</year></dates><pub-location>Research Triangle Park, NC</pub-location><isbn>Toxicity Report 96</isbn><label>5400978</label><urls><related-urls><url>https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox096_508.pdf</url></related-urls></urls><language>English</language><modified-date>National Toxicology Program</modified-date></record></Cite></EndNote>]. Note that a complete spermatogenesis cycle in male rats is typically 7 weeks in length, thus study designs of shorter duration could potentially miss effects of chemical exposure on some sperm parameters. Accordingly, the differences in responses observed in the two available studies might have been due to experimental design differences, because [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578545"] exposed P_0 animals for 70 days and F_1 animals during the entire period of gestation plus lactation, whereas [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5400978"] exposed animals for 28 days. Future studies should be conducted to determine whether long-term and/or gestational exposure to PFBS significantly affects sperm measures in sexually mature and developing animals.

4.2.2.3 Reproductive Hormones (Female and Male)

Reproductive hormones were evaluated in mice [ADDIN EN.CITE <EndNote><Cite><Author>Feng</Author><Year>2017</Year><RecNum>1031</RecNum><IDText>3856465</IDText><DisplayText>(Feng et al., 2017)</DisplayText><record><rec-number>1031</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1031</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Feng, X.</author><author>Cao, X.</author><author>Zhao, S.</author><author>Wang, X.</author><author>Hua, X.</author><author>Chen, L.</author><author>Chen, L.</author></authors></contributors><titles><title>Exposure of pregnant mice to perfluorobutanesulfonate causes hypothyroxinemia and developmental abnormalities in female offspring</title><secondary-title>Toxicological Sciences</secondary-title><alt-title>Toxicol Sci</alt-title><short-title>Toxicological Sciences</short-title></titles><periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></periodical><alt-periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></alt-periodical><pages>409-419</pages><volume>155</volume><number>2</number><dates><year>2017</year></dates><isbn>ISSN 1096-6080
EISSN 1096-0929</isbn><accession-num>27803384</accession-num><label>3856465</label><urls><related-urls><url>http://dx.doi.org/10.1093/toxsci/kfw219</url></related-urls></urls><electronic-

resource-num>10.1093/toxsci/kfw219</electronic-resource-num><language>English</language></record></Cite></EndNote>] and, to a limited extent, in rats [ADDIN EN.CITE <EndNote><Cite><Author>NTP</Author><Year>2019</Year><RecNum>1223</RecNum><IDText>5400978</IDText><DisplayText>(NTP, 2019)</DisplayText><record><rec-number>1223</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1223</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NTP,</author></authors></contributors><titles><title>NTP technical report on the toxicity studies of perfluoroalkyl sulfonates (perfluorobutane sulfonic acid, perfluorohexane sulfonate potassium salt, and perfluorooctane sulfonic acid) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats</title></titles><dates><year>2019</year></dates><pub-location>Research Triangle Park, NC</pub-location><isbn>Toxicity Report 96</isbn><label>5400978</label><urls><related-urls><url>https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox096_508.pdf</url></related-urls></urls><language>English</language><modified-date>National Toxicology Program</modified-date></record></Cite></EndNote>] (see [REF _Ref55814618 \h]). Exposure to K^{+}PFBS for 28 days resulted in a significant trend for increased testosterone levels in females, but not in males [ADDIN EN.CITE <EndNote><Cite><Author>NTP</Author><Year>2019</Year><RecNum>1223</RecNum><IDText>5400978</IDText><DisplayText>(NTP, 2019)</DisplayText><record><rec-number>1223</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1223</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NTP,</author></authors></contributors><titles><title>NTP technical report on the toxicity studies of perfluoroalkyl sulfonates (perfluorobutane sulfonic acid, perfluorohexane sulfonate potassium salt, and perfluorooctane sulfonic acid) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats</title></titles><dates><year>2019</year></dates><pub-location>Research Triangle Park, NC</pub-location><isbn>Toxicity Report 96</isbn><label>5400978</label><urls><related-urls><url>https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox096_508.pdf</url></related-urls></urls><language>English</language><modified-date>National Toxicology Program</modified-date></record></Cite></EndNote>]. The increase in testosterone was not statistically significant when compared to control at any dose by pairwise analysis. Prenatal exposure to PFBS at and above 200 mg/kg-day resulted in statistically significant reduced serum estradiol levels and increased serum luteinizing hormone levels in pubertal offspring (i.e., PND 30) [ADDIN EN.CITE <EndNote><Cite><Author>Feng</Author><Year>2017</Year><RecNum>1031</RecNum><IDText>3856465</IDText><DisplayText>(Feng et al., 2017)</DisplayText><record><rec-number>1031</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1031</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Feng, X.</author><author>Cao, X.</author><author>Zhao, S.</author><author>Wang, X.</author><author>Hua, X.</author><author>Chen, L.</author><author>Chen, L.</author></authors></contributors><titles><title>Exposure of pregnant mice to perfluorobutanesulfonate causes hypothyroxinemia and developmental abnormalities in female

offspring</title><secondary-title>Toxicological Sciences</secondary-title><alt-title>Toxicol Sci</alt-title><short-title>Toxicological Sciences</short-title></titles><periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></periodical><alt-periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></alt-periodical><pages>409-419</pages><volume>155</volume><number>2</number><dates><year>2017</year></dates><isbn>ISSN 1096-6080
EISSN 1096-0929</isbn><accession-num>27803384</accession-num><label>3856465</label><urls><related-urls><url>http://dx.doi.org/10.1093/toxsci/kfw219</url></related-urls></urls><electronic-resource-num>10.1093/toxsci/kfw219</electronic-resource-num><language>English</language></record></Cite></EndNote>]. The change in serum estradiol levels, but not luteinizing hormone, continued into adulthood in the K^+PFBS-exposed offspring (i.e., PND 60). Adult PFBS-exposed offspring also exhibited decreased serum progesterone levels at doses of 200 mg/kg-day and greater. PFBS exposure did not alter maternal estradiol-, progesterone-, or gonadotropin-releasing hormone. Reproductive hormone levels in males and females were not evaluated by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578545"]. The changes in follicle and corpora lutea development reported in the same study, however, may be associated with alterations in hormone production/levels because ovarian follicles and corpora lutea produce estrogen and progesterone, respectively [ADDIN EN.CITE ADDIN EN.CITE.DATA].

The hormonal effects observed in the [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5400978"] and [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"] studies might be associated with adverse reproductive effects reported in these studies. Androgens, luteinizing hormone, estradiol, and progesterone play an important role in normal development and in the functioning of the female reproductive system [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Alterations in the levels and production of these reproductive hormones can disrupt endocrine signals at the hypothalamic-pituitary level and lead to delayed reproductive development and changes in functions [ADDIN EN.CITE ADDIN EN.CITE.DATA].

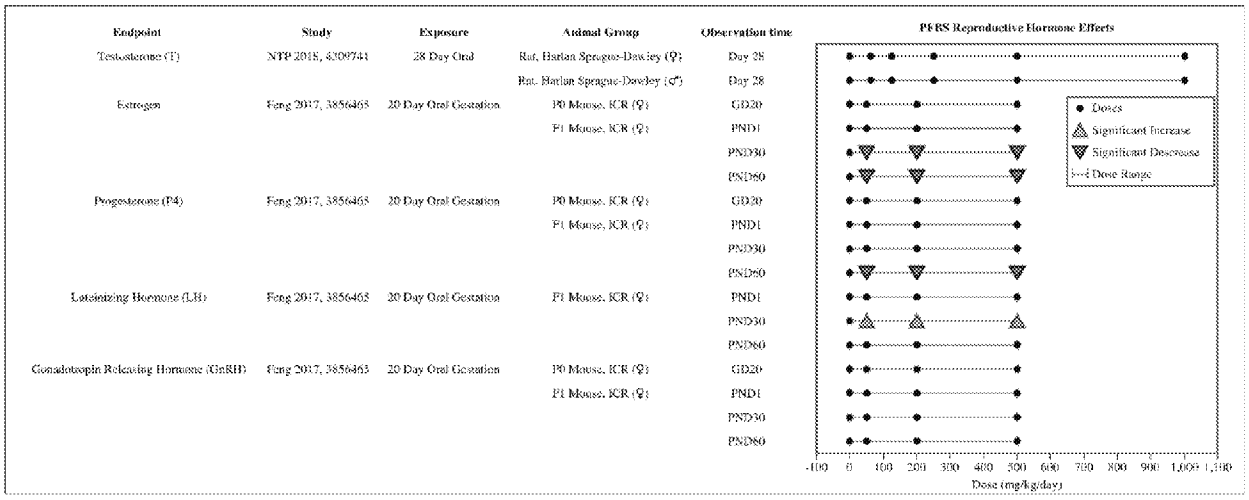

Figure [SEQ Figure * ARABIC]. Reproductive Hormone Response to K^+PFBS Exposure (Click to see interactive data graphic and rationale for study evaluations for [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-reproductive-hormone-effects2/"] in HAWC)

4.2.2.4 Reproductive System Development, Including Markers of Sexual Differentiation and Maturation (Female and Male)

Several measures of female reproductive development were affected by gestational K^+PFBS exposure in mice (see [REF _Ref55814644 \h], [REF _Ref55819352 \h], and [REF _Ref55819357 \h]). [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"] reported a delayed first estrous in female PFBS-exposed offspring (≥200 mg/kg-day) compared with control (see [REF _Ref55819352 \h]). Estrous cyclicity was also affected in K^+PFBS-exposed PNDs 40−60 offspring as exhibited by a prolongation of the diestrus stage compared with control. Estrous cycling was generally not statistically significantly altered in P_0- or F_1-generation females treated with K^+PFBS in the two-generation study by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578545"]. An increase in the number of rats with ≥6 consecutive days of diestrus was observed in the F_1 females exposed to 100 mg/kg-day; however, the increase was not present at higher doses [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1044</RecNum><IDText>1578545</IDText><DisplayText>(Lieder et al., 2009b)</DisplayText><record><rec-number>1044</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1044</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lieder, P. H.</author><author>York, R. G.</author><author>Hakes, D. C.</author><author>Chang, S. C.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>A two-generation oral gavage reproduction study with potassium perfluorobutanesulfonate (K+PFBS) in Sprague Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-

title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>33-45</pages><volume>259</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>19428941</accession-num><label>1578545</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2009.01.027</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2009.01.027</electronic-resource-num><language>English</language></record></Cite></EndNote>]. Estrous cyclicity was affected after adult exposure to K^+PFBS for 28 days as shown by a dose-dependent prolongation of diestrus at doses of 250 mg/kg-day and greater with marginal significance at the lowest dose tested (125 mg/kg-day) ($p = 0.063$) [ADDIN EN.CITE <EndNote><Cite><Author>NTP</Author><Year>2019</Year><RecNum>1223</RecNum><IDText>5400978</IDText><DisplayText>(NTP, 2019)</DisplayText><record><rec-number>1223</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1223</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NTP,</author></authors></contributors><titles><title>NTP technical report on the toxicity studies of perfluoroalkyl sulfonates (perfluorobutane sulfonic acid, perfluorohexane sulfonate potassium salt, and perfluorooctane sulfonic acid) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats</title></titles><dates><year>2019</year></dates><pub-location>Research Triangle Park, NC</pub-location><isbn>Toxicity Report 96</isbn><label>5400978</label><urls><related-urls><url>https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox096_508.pdf</url></related-urls></urls><language>English</language><modified-date>National Toxicology Program</modified-date></record></Cite></EndNote>]. [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578545"] reported a delay in the days to preputial separation in F_1 males of the 30- and 1,000-mg/kg-day groups;[10]

[10]A marker of delayed reproductive development [ADDIN EN.CITE <EndNote><Cite><Author>Foster</Author><Year>2013</Year><RecNum>1298</RecNum><IDText>2993402</IDText><DisplayText>(Foster and Gray, 2013; U.S. EPA, 1996a)</DisplayText><record><rec-number>1298</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1298</key></foreign-keys><ref-type name="Edited Book">28</ref-type><contributors><authors><author>Foster, P.</author><author>Gray, L. E., Jr</author></authors><secondary-authors><author>Klaassen, C. D.</author></secondary-authors></contributors><titles><title>Toxic responses of the reproductive system</title><secondary-title>Casarett & Doull's toxicology: The basic science of poisons</secondary-title></titles><pages>861-906</pages><edition>8th</edition><dates><year>2013</year></dates><pub-location>New York, NY</pub-location><publisher>McGraw-Hill Education</publisher><label>2993402</label><urls><related-urls><url>https://www.mheducation.com/highered/product/casarett-doull-s-toxicology-basic-science-poisons-9th-edition-klaassen/9781259863745.html</url></related-urls></urls></record></Cite><Cite><Author>U.S. EPA</Author><Year>1996</Year><RecNum>1319</RecNum><IDText>30019</IDText><record><rec-number>1319</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1319</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Guidelines for reproductive toxicity risk assessment</title></titles><pages>1-143</pages><dates><year>1996</year></dates><pub-location>Washington, DC</pub-location><publisher>U.S. Environmental Protection Agency, Risk Assessment Forum</publisher><isbn>EPA/630/R-96/009</isbn><label>30019</label><urls><related-urls><url>https://www.epa.gov/sites/production/files/2014-

however, the measure was no longer statistically significant when adjusted for BW. There was similarly no change in the days to vaginal patency in F_1 female rats [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1044</RecNum><IDText>1578545</IDText><DisplayText>(Lieder et al., 2009b)</DisplayText><record><rec-number>1044</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1044</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lieder, P. H.</author><author>York, R. G.</author><author>Hakes, D. C.</author><author>Chang, S. C.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>A two-generation oral gavage reproduction study with potassium perfluorobutanesulfonate (K+PFBS) in Sprague Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>33-45</pages><volume>259</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>19428941</accession-num><label>1578545</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2009.01.027</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2009.01.027</electronic-resource-num><language>English</language></record></Cite></EndNote>]. Unlike [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578545"], [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"] reported a delay in vaginal patency in F_1 females after gestational exposure of 200 mg/kg-day and greater (see [REF _Ref55819357 \h]).

11/documents/guidelines_repro_toxicity.pdf</url></related-urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>].

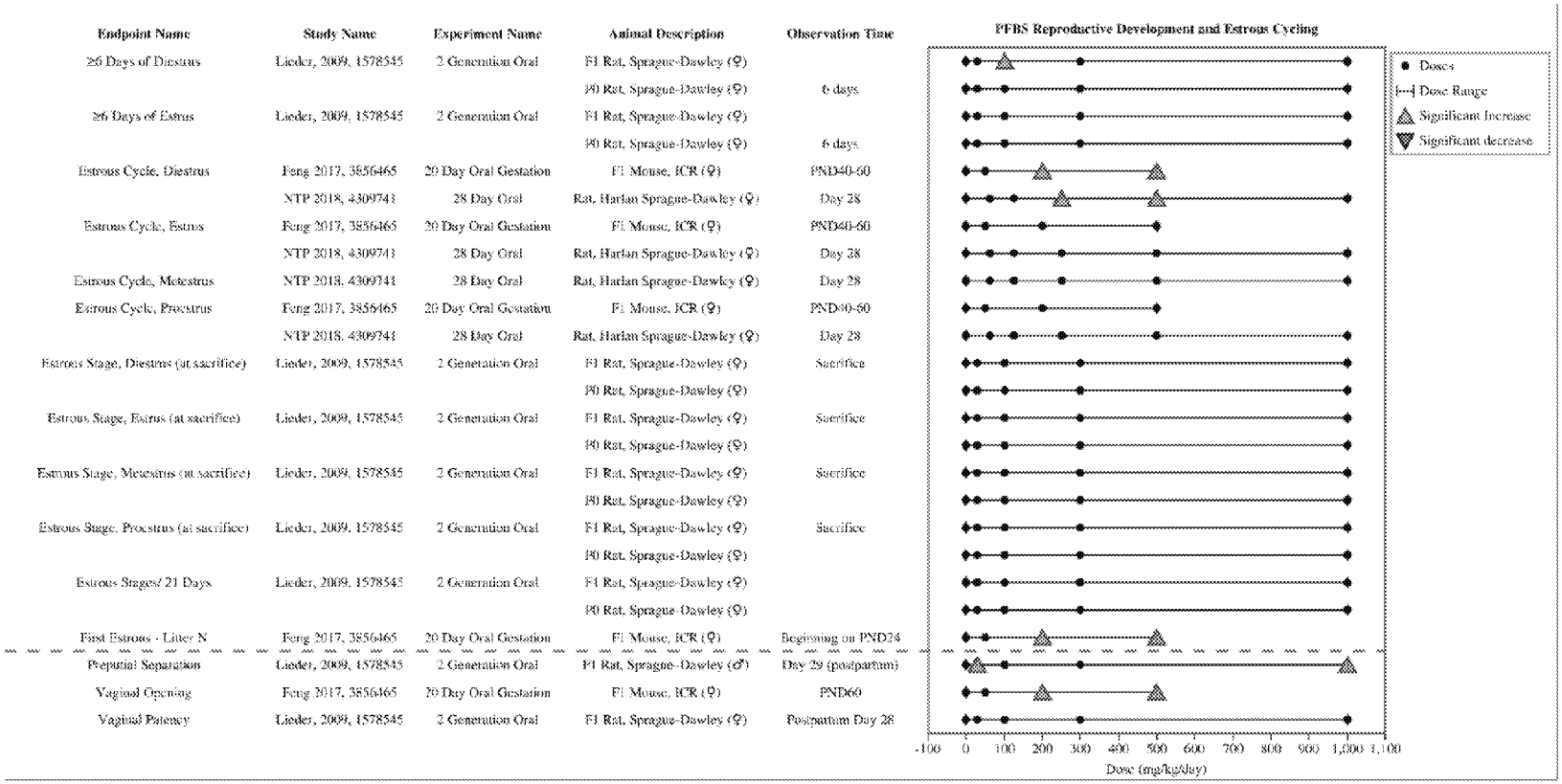

Figure [SEQ Figure * ARABIC]. Effects on Reproductive Development and Estrous Cycling Following PFBS Exposure (Click to see [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-reproductive-development/"])

4.2.2.5 Reproductive Organ Weights and Histopathology (Female and Male)

Studies have not consistently reported changes in reproductive organ weights (click to see interactive graphic for [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-reproductive-organ-effects/"] in HAWC). Reproductive organ weights, including testes, ovaries, and uterus, were unchanged in the two-generation reproductive study in P_0 and F_1 males and females [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1044</RecNum><IDText>1578545</IDText><DisplayText>(Lieder et al., 2009b)</DisplayText><record><rec-number>1044</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1044</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lieder, P. H.</author><author>York, R. G.</author><author>Hakes, D. C.</author><author>Chang, S. C.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>A two-generation oral gavage reproduction study with potassium perfluorobutanesulfonate (K+PFBS) in Sprague Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>33-45</pages><volume>259</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>19428941</accession-num><label>1578545</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2009.01.027</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2009.01.027</electronic-resource-num><language>English</language></record></Cite></EndNote>] and following short-term and subchronic exposure to K^+PFBS [ADDIN EN.CITE ADDIN EN.CITE.DATA]. F_1 females gestationally exposed to PFBS, however, exhibited decreased size and weight of the ovaries and uterus [ADDIN EN.CITE <EndNote><Cite><Author>Feng</Author><Year>2017</Year><RecNum>1031</RecNum><IDText>3856465</IDText><DisplayText>(Feng et al., 2017)</DisplayText><record><rec-number>1031</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1031</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Feng, X.</author><author>Cao, X.</author><author>Zhao, S.</author><author>Wang, X.</author><author>Hua, X.</author><author>Chen, L.</author><author>Chen, L.</author></authors></contributors><titles><title>Exposure of pregnant mice to perfluorobutanesulfonate causes hypothyroxinemia and developmental abnormalities in female offspring</title><secondary-title>Toxicological Sciences</secondary-title><alt-title>Toxicol Sci</alt-title><short-title>Toxicological Sciences</short-title></titles><periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></periodical><alt-periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></alt-periodical><pages>409-419</pages><volume>155</volume><number>2</number><dates><year>2017</year></dates><isbn>ISSN 1096-6080
EISSN 1096-0929</isbn><accession-num>27803384</accession-num><label>3856465</label><urls><related-urls><url>http://dx.doi.org/10.1093/toxsci/kfw219</url></related-urls></urls><electronic-

resource-num>10.1093/toxsci/kfw219</electronic-resource-num><language>English</language></record></Cite></EndNote>]. In addition, the total uterine section diameter and endometrial and myometrial thickness were significantly reduced. There were no significant histopathological alterations in the male or female reproductive organs evaluated following exposure to K^+PFBS for 28 days [ADDIN EN.CITE <EndNote><Cite><Author>NTP</Author><Year>2019</Year><RecNum>1223</RecNum><IDText>5400978</IDText><DisplayText>(NTP, 2019)</DisplayText><record><rec-number>1223</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1223</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NTP,</author></authors></contributors><titles><title>NTP technical report on the toxicity studies of perfluoroalkyl sulfonates (perfluorobutane sulfonic acid, perfluorohexane sulfonate potassium salt, and perfluorooctane sulfonic acid) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats</title></titles><dates><year>2019</year></dates><pub-location>Research Triangle Park, NC</pub-location><isbn>Toxicity Report 96</isbn><label>5400978</label><urls><related-urls><url>https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox096_508.pdf</url></related-urls></urls><language>English</language><modified-date>National Toxicology Program</modified-date></record></Cite></EndNote>] or in parental or offspring from the two-generation reproductive study [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1044</RecNum><IDText>1578545</IDText><DisplayText>(Lieder et al., 2009b)</DisplayText><record><rec-number>1044</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1044</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lieder, P. H.</author><author>York, R. G.</author><author>Hakes, D. C.</author><author>Chang, S. C.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>A two-generation oral gavage reproduction study with potassium perfluorobutanesulfonate (K+PFBS) in Sprague Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>33-45</pages><volume>259</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>19428941</accession-num><label>1578545</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2009.01.027</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2009.01.027</electronic-resource-num><language>English</language></record></Cite></EndNote>].

4.3 OFFSPRING GROWTH AND EARLY DEVELOPMENT

4.3.1 Human Studies

No human studies were available to inform the potential for PFBS exposure to cause effects on the growth or early development of children.

4.3.2 Animal Studies

Evidence to inform organ/system-specific effects of PFBS in animals following developmental exposure are discussed in the individual hazard sections (e.g., reproductive cycling after developmental exposure is discussed in the "Reproductive Effects" section). This section is limited to discussion of other, specific developmental effects commonly evaluated in guideline developmental toxicity studies, including pup BW, developmental markers, and bone measures. Four high- or medium-confidence studies examined potential alterations in offspring growth and early development following PFBS exposure, including two gestational exposure studies in rats [ADDIN EN.CITE
<EndNote><Cite><Author>York</Author><Year>2002</Year><RecNum>1261</RecNum><IDText>4289675</IDText><DisplayText>(York, 2003a, 2002)</DisplayText><record><rec-number>1261</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1261</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>York, R. G.</author></authors></contributors><titles><title>Oral (gavage) developmental toxicity study of potassium perfluorobutane sulfonate (PFBS) in rats</title></titles><dates><year>2002</year></dates><pub-location>St. Paul, MN</pub-location><publisher>3M Corporate Toxicology</publisher><isbn>Argus Research Protocol Number 418-023</isbn><label>4289675</label><urls></urls><language>English</language></record></Cite><Cite><Author>York</Author><Year>2003</Year><RecNum>1248</RecNum><IDText>4322522</IDText><record><rec-number>1248</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1248</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>York, R. G.</author></authors></contributors><titles><title>Oral (galvage) dosage-range developmental toxicity study of potassium perfluorobutane sulfonate (PFBS) in rats</title></titles><dates><year>2003</year></dates><pub-location>Horsham, PA</pub-location><publisher>Argus Research</publisher><isbn>Sponsor's study no. T-7485.11</isbn><label>4322522</label><urls></urls><language>English</language></record></Cite></EndNote>] and one gestational exposure study in mice [ADDIN EN.CITE
<EndNote><Cite><Author>Feng</Author><Year>2017</Year><RecNum>1031</RecNum><IDText>3856465</IDText><DisplayText>(Feng et al., 2017)</DisplayText><record><rec-number>1031</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1031</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Feng, X.</author><author>Cao, X.</author><author>Zhao, S.</author><author>Wang, X.</author><author>Hua, X.</author><author>Chen, L.</author><author>Chen, L.</author></authors></contributors><titles><title>Exposure of pregnant mice to perfluorobutanesulfonate causes hypothyroxinemia and developmental abnormalities in female offspring</title><secondary-title>Toxicological Sciences</secondary-title><alt-title>Toxicol Sci</alt-title><short-title>Toxicological Sciences</short-title></titles><periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></periodical><alt-periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></alt-periodical><pages>409-419</pages><volume>155</volume><number>2</number><dates><year>2017</year></dates><isbn>ISSN 1096-6080
EISSN 1096-0929</isbn><accession-num>27803384</accession-

num><label>3856465</label><urls><related-urls><url>http://dx.doi.org/10.1093/toxsci/kfw219</url></related-urls></urls><electronic-resource-num>10.1093/toxsci/kfw219</electronic-resource-num><language>English</language></record></Cite></EndNote>], as well as a two-generation study in rats [ADDIN EN.CITE ADDIN EN.CITE.DATA]. (Click to see interactive graphic for [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-developmental-effects/"] in HAWC.)

None of the studies identified significant effects in either rats or mice on measures of fetal morphology (i.e., malformations and variations). BW of female offspring of PFBS-exposed mice at doses greater than 200 mg/kg-day was statistically significantly lower than control at PND 1, and the pups remained underweight through weaning, pubertal, and adult periods, with decreases of approximately 25% observable in pups nearing weaning [ADDIN EN.CITE <EndNote><Cite><Author>Feng</Author><Year>2017</Year><RecNum>1031</RecNum><IDText>3856465</IDText><DisplayText>(Feng et al., 2017)</DisplayText><record><rec-number>1031</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1031</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Feng, X.</author><author>Cao, X.</author><author>Zhao, S.</author><author>Wang, X.</author><author>Hua, X.</author><author>Chen, L.</author><author>Chen, L.</author></authors></contributors><titles><title>Exposure of pregnant mice to perfluorobutanesulfonate causes hypothyroxinemia and developmental abnormalities in female offspring</title><secondary-title>Toxicological Sciences</secondary-title><alt-title>Toxicol Sci</alt-title><short-title>Toxicological Sciences</short-title></titles><periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></periodical><alt-periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></alt-periodical><pages>409-419</pages><volume>155</volume><number>2</number><dates><year>2017</year></dates><isbn>ISSN 1096-6080
EISSN 1096-0929</isbn><accession-num>27803384</accession-num><label>3856465</label><urls><related-urls><url>http://dx.doi.org/10.1093/toxsci/kfw219</url></related-urls></urls><electronic-resource-num>10.1093/toxsci/kfw219</electronic-resource-num><language>English</language></record></Cite></EndNote>]. At around PND 16, [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"] also reported an ~1.5-day developmental delay in eye opening in pups gestationally exposed to 200 mg/kg-day PFBS and greater. Importantly, no effects on the health of the exposed dams (e.g., weight gain) were observed at any dose [ADDIN EN.CITE <EndNote><Cite><Author>Feng</Author><Year>2017</Year><RecNum>1031</RecNum><IDText>3856465</IDText><DisplayText>(Feng et al., 2017)</DisplayText><record><rec-number>1031</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1031</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Feng, X.</author><author>Cao, X.</author><author>Zhao, S.</author><author>Wang, X.</author><author>Hua, X.</author><author>Chen, L.</author><author>Chen, L.</author></authors></contributors><titles><title>Exposure of pregnant mice to

perfluorobutanesulfonate causes hypothyroxinemia and developmental abnormalities in female offspring</title><secondary-title>Toxicological Sciences</secondary-title><alt-title>Toxicol Sci</alt-title><short-title>Toxicological Sciences</short-title></titles><periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></periodical><alt-periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></alt-periodical><pages>409-419</pages><volume>155</volume><number>2</number><dates><year>2017</year></dates><isbn>ISSN 1096-6080
EISSN 1096-0929</isbn><accession-num>27803384</accession-num><label>3856465</label><urls><related-urls><url>http://dx.doi.org/10.1093/toxsci/kfw219</url></related-urls></urls><electronic-resource-num>10.1093/toxsci/kfw219</electronic-resource-num><language>English</language></record></Cite></EndNote>]. [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-eye-opening-effect-size-animal/"] for eye opening, including effect size and variability, are included in Appendix E, [REF _Ref55819340 \h]. Fetal BWs (male and female) were also reduced (approximately 10%) compared with controls following gestational exposure from GDs 6 to 20 at the highest tested dose (1,000 mg/kg-day in [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=4289675"] and 2,000 mg/kg-day in [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=4322522"]]). Parental BWs and organ weights, however, were also affected to a similar degree at those doses [ADDIN EN.CITE ADDIN EN.CITE.DATA], limiting the interpretation of the results. No statistically significant changes in F_1- and F_2-generation pup mean pup weight at birth and mean pup weight at weaning were reported by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578545"] or [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=4289686"].

Several measures of thyroid hormone development and female reproductive development were affected by gestational PFBS exposure in mice and are described in more detail in the "Thyroid Effects" and "Reproductive Effects" sections, respectively.

4.4 RENAL EFFECTS

4.4.1 Human Studies

One [HYPERLINK "https://hawcprd.epa.gov/rob/study/100001468/"] study ([HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3981721"], with additional details in [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=2324901"], selected 225 subjects ages 12−15 years old from a prior cohort study population in seven public schools in northern Taiwan [ADDIN EN.CITE <EndNote><Cite><Author>Tsai</Author><Year>2010</Year><RecNum>1017</RecNum><IDText>2333532</IDText><DisplayText>(Tsai et al., 2010)</DisplayText><record><rec-number>1017</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1017</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Tsai,

C.</author><author>Huang, J.</author><author>Hwang, B. F.</author><author>Lee, Y. L.</author></authors></contributors><titles><title>Household environmental tobacco smoke and risks of asthma, wheeze and bronchitic symptoms among children in Taiwan</title><secondary-title>Respiratory Research</secondary-title><alt-title>Respir Res</alt-title><short-title>Respiratory Research</short-title></titles><periodical><full-title>Respiratory Research</full-title><abbr-1>Respir Res</abbr-1></periodical><alt-periodical><full-title>Respiratory Research</full-title><abbr-1>Respir Res</abbr-1></alt-periodical><pages>11</pages><volume>11</volume><dates><year>2010</year></dates><isbn>ISSN 1465-9921
EISSN 1465-993X</isbn><accession-num>20113468</accession-num><label>2333532</label><urls><related-urls><url>http://dx.doi.org/10.1186/1465-9921-11-11</url></related-urls></urls><electronic-resource-num>10.1186/1465-9921-11-11</electronic-resource-num><language>English</language></record></Cite></EndNote>] and examined the association between PFBS exposure and uric acid concentrations. There was no association between ln(PFBS) concentration and uric acid concentrations in the total population (β: 0.0064 mg/dL increase in uric acid per 1 ln-μg/L increase in PFBS; 95% CI: −0.22−0.23). U.S. EPA identified that a nonsignificant positive association in boys was offset by a nonsignificant negative association in girls, and there is not enough information to determine whether there is a sex dependence. When PFBS exposure was analyzed for high uric acid (>6 mg/dL), the risk was somewhat elevated in boys (OR: 1.53; 95% CI: 0.92−2.54), but not in girls (OR: 0.99; 95% CI: 0.58−1.73). The potential for reverse causation (i.e., that renal function could influence the levels of PFBS in the blood) tempers any conclusions that might be drawn.

4.4.2 Animal Studies

Renal effects were evaluated in high-confidence short-term and subchronic-duration exposure studies in rats [ADDIN EN.CITE ADDIN EN.CITE.DATA] and in a high-confidence two-generation reproductive study in rats [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1044</RecNum><IDText>1578545</IDText><DisplayText>(Lieder et al., 2009b)</DisplayText><record><rec-number>1044</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1044</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lieder, P. H.</author><author>York, R. G.</author><author>Hakes, D. C.</author><author>Chang, S. C.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>A two-generation oral gavage reproduction study with potassium perfluorobutanesulfonate (K+PFBS) in Sprague Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>33-45</pages><volume>259</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>19428941</accession-num><label>1578545</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2009.01.027</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2009.01.027</electronic-resource-num><language>English</language></record></Cite></EndNote>]. Endpoints evaluated in

these studies include kidney weights, histopathological changes, and serum biomarkers of effect (see [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-kidney-effects-kris-v3/"] and [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-renal-effects-2/"]). Dose-response graphics for histopathological effects, including effect size and variability, are included in Appendix E, [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-kidney-histopathology-effect-size-animal/"].

Absolute and relative kidney weights of males and females were unchanged in S-D rats exposed daily for 90 days to K^+PFBS at doses up to 600 mg/kg-day compared with control rats [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1043</RecNum><IDText>1578546</IDText><DisplayText>(Lieder et al., 2009a)</DisplayText><record><rec-number>1043</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1043</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lieder, P. H.</author><author>Chang, S. C.</author><author>York, R. G.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>Toxicological evaluation of potassium perfluorobutanesulfonate in a 90-day oral gavage study with Sprague-Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>45-52</pages><volume>255</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>18992301</accession-num><label>1578546</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2008.10.002</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2008.10.002</electronic-resource-num><language>English</language></record></Cite></EndNote>]. This lack of effect on kidney weight was also observed in parental and F_1 male and female rats of the same strain exposed to K^+PFBS at doses up to 1,000 mg/kg-day during a two-generation reproductive study [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1044</RecNum><IDText>1578545</IDText><DisplayText>(Lieder et al., 2009b)</DisplayText><record><rec-number>1044</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1044</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lieder, P. H.</author><author>York, R. G.</author><author>Hakes, D. C.</author><author>Chang, S. C.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>A two-generation oral gavage reproduction study with potassium perfluorobutanesulfonate (K+PFBS) in Sprague Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>33-

45</pages><volume>259</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>19428941</accession-num><label>1578545</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2009.01.027</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2009.01.027</electronic-resource-num><language>English</language></record></Cite></EndNote>]. Although none of the findings reached statistical significance, an approximate 9% increase in absolute kidney weight was observed in female S-D rats exposed to 1,000 mg/kg-day K^+PFBS for 10 days [ADDIN EN.CITE <EndNote><Cite><Author>3M</Author><Year>2000</Year><RecNum>1257</RecNum><IDText>4289992</IDText><DisplayText>(3M, 2000d)</DisplayText><record><rec-number>1257</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1257</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>3M,</author></authors></contributors><titles><title>A repeated dose range-finding toxicity study of T-7485 in Sprague-Dawley rats</title></titles><dates><year>2000</year></dates><pub-location>St. Paul, MN</pub-location><publisher>3M Pharmaceuticals</publisher><isbn>Study Number: 132-006</isbn><label>4289992</label><urls></urls><language>English</language><modified-date>3M Company</modified-date></record></Cite></EndNote>]; relative-to-body kidney weights were also increased approximately 6–9%. This organ-weight effect was not observed in corresponding males of the study. In a follow-up 28-day study by the same lab, a 9–11% increase in absolute and relative-to-body kidney weight was observed in female S-D rats exposed to 900 mg/kg-day K^+PFBS [ADDIN EN.CITE <EndNote><Cite><Author>3M</Author><Year>2001</Year><RecNum>602</RecNum><IDText>4241246</IDText><DisplayText>(3M, 2001)</DisplayText><record><rec-number>602</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604955602">602</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>3M,</author></authors></contributors><titles><title>A 28-day oral (gavage) toxicity study of T-7485 in Sprague-Dawley rats</title></titles><dates><year>2001</year></dates><pub-location>St. Paul, MN</pub-location><publisher>3M Corporate Toxicology</publisher><isbn>Study Number: 132-007</isbn><label>4241246</label><urls></urls><language>English</language><modified-date>3M Company</modified-date></record></Cite></EndNote>], although these changes were not statistically significant. In this study, U.S. EPA also observed that smaller nonsignificant increases in kidney weight occurred in male rats. In another 28-day study, K^+PFBS exposure significantly increased absolute and relative right kidney weights in high-dose (500 mg/kg-day) male S-D rats [ADDIN EN.CITE <EndNote><Cite><Author>NTP</Author><Year>2019</Year><RecNum>1223</RecNum><IDText>5400978</IDText><DisplayText>(NTP, 2019)</DisplayText><record><rec-number>1223</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1223</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NTP,</author></authors></contributors><titles><title>

NTP technical report on the toxicity studies of perfluoroalkyl sulfonates (perfluorobutane sulfonic acid, perfluorohexane sulfonate potassium salt, and perfluorooctane sulfonic acid) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats</title></titles><dates><year>2019</year></dates><pub-location>Research Triangle Park, NC</pub-location><isbn>Toxicity Report 96</isbn><label>5400978</label><urls><related-urls><url>https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox096_508.pdf</url></related-urls></urls><language>English</language><modified-date>National Toxicology Program</modified-date></record></Cite></EndNote>]. Only relative kidney weights were altered in female rats, but this effect was significant at all tested K^+PFBS doses (≥62.6 mg/kg-day). Click to see interactive graphic for [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-renal-effects-2/"] in HAWC.

After 90 days of exposure, [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578546"] observed increased incidences of histopathological alterations of the kidneys of male and female rats of the high-dose group (600 mg/kg-day). Increased incidence of [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-kidney-histopathology-effect-size-animal/"] of the epithelium of renal papillary tubules and ducts was observed in rats of both sexes (see [REF _Ref55819447 \h][REF _Ref55819448 \h]). A single incidence of papillary necrosis in both kidneys was observed in one male in the high-dose group. Further, focal papillary edema was observed in 3/10 rats of both sexes of the high-dose groups compared with no evidence of this effect in control rats. Similar histopathological alterations were observed in parental and F_1 male and female rats in the two-generation reproduction study [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1044</RecNum><IDText>1578545</IDText><DisplayText>(Lieder et al., 2009b)</DisplayText><record><rec-number>1044</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1044</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lieder, P. H.</author><author>York, R. G.</author><author>Hakes, D. C.</author><author>Chang, S. C.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>A two-generation oral gavage reproduction study with potassium perfluorobutanesulfonate (K+PFBS) in Sprague Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>33-45</pages><volume>259</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>19428941</accession-num><label>1578545</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2009.01.027</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2009.01.027</electronic-resource-num><language>English</language></record></Cite></EndNote>]. Compared with control rats, increased incidences of [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-kidney-histopathology-effect-size-animal/"] of the renal

tubular and ductal papillary epithelium, and focal papillary edema were observed in parental male and female rats at PFBS doses ≥300 mg/kg-day. Hyperplastic foci in the same locations of the kidney were also observed in male and female F_1 rats exposed to ≥300 mg/kg-day PFBS across life stages from gestation to adulthood [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1044</RecNum><IDText>1578545</IDText><DisplayText>(Lieder et al., 2009b)</DisplayText><record><rec-number>1044</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1044</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lieder, P. H.</author><author>York, R. G.</author><author>Hakes, D. C.</author><author>Chang, S. C.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>A two-generation oral gavage reproduction study with potassium perfluorobutanesulfonate (K+PFBS) in Sprague Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>33-45</pages><volume>259</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>19428941</accession-num><label>1578545</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2009.01.027</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2009.01.027</electronic-resource-num><language>English</language></record></Cite></EndNote>]. Focal papillary edema was observed in male (≥1,000 mg/kg-day) and female (≥300 mg/kg-day) F_1 rats, although this specific alteration did not appear to be dose-dependent in females. Although kidney alterations such as hydronephrosis, mineralization, and tubular degeneration were observed in male or female S-D rats after just 10 days of oral K^+PFBS exposure, these effects were not significant compared to control and/or did not appear to be dose-dependent [ADDIN EN.CITE <EndNote><Cite><Author>3M</Author><Year>2000</Year><RecNum>1257</RecNum><IDText>4289992</IDText><DisplayText>(3M, 2000d)</DisplayText><record><rec-number>1257</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1257</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>3M,</author></authors></contributors><titles><title>A repeated dose range-finding toxicity study of T-7485 in Sprague-Dawley rats</title></titles><dates><year>2000</year></dates><pub-location>St. Paul, MN</pub-location><publisher>3M Pharmaceuticals</publisher><isbn>Study Number: 132-006</isbn><label>4289992</label><urls></urls><language>English</language><modified-date>3M Company</modified-date></record></Cite></EndNote>]. The same histopathological lesions were noted in the 28-day rat study albeit with lack of statistical significance compared to control [ADDIN EN.CITE <EndNote><Cite><Author>3M</Author><Year>2001</Year><RecNum>602</RecNum><IDText>4241246</IDText><DisplayText>(3M, 2001)</DisplayText><record><rec-number>602</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604955602">602</key></foreign-keys><ref-type name="Report">27</ref-

type><contributors><authors><author>3M,</author></authors></contributors><titles><title>A 28-day oral (gavage) toxicity study of T-7485 in Sprague-Dawley rats</title></titles><dates><year>2001</year></dates><pub-location>St. Paul, MN</pub-location><publisher>3M Corporate Toxicology</publisher><isbn>Study Number: 132-007</isbn><label>4241246</label><urls></urls><language>English</language><modified-date>3M Company</modified-date></record></Cite></EndNote>]. In another 28-day gavage study in S-D rats, chronic progressive nephropathy (CPN) was observed in all male and female PFBS treatment groups and control rats, with no evidence of dose dependence for this effect [ADDIN EN.CITE <EndNote><Cite><Author>NTP</Author><Year>2019</Year><RecNum>1223</RecNum><IDText>5400978</IDText><DisplayText>(NTP, 2019)</DisplayText><record><rec-number>1223</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1223</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NTP,</author></authors></contributors><titles><title>NTP technical report on the toxicity studies of perfluoroalkyl sulfonates (perfluorobutane sulfonic acid, perfluorohexane sulfonate potassium salt, and perfluorooctane sulfonic acid) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats</title></titles><dates><year>2019</year></dates><pub-location>Research Triangle Park, NC</pub-location><isbn>Toxicity Report 96</isbn><label>5400978</label><urls><related-urls><url>https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox096_508.pdf</url></related-urls></urls><language>English</language><modified-date>National Toxicology Program</modified-date></record></Cite></EndNote>]. Renal papillary necrosis was also observed in these rats but only at the highest exposure dose (1,000 mg/kg-day).

Serum levels of biomarkers indicative of kidney injury and/or function, including blood urea nitrogen (BUN) and creatinine, have been examined across multiple studies of varying exposure durations, and were found to be unchanged in male and female rats treated with K^+PFBS at doses up to 1,000 mg/kg-day [ADDIN EN.CITE ADDIN EN.CITE.DATA]. After 28 days of gavage exposure in S-D rats, however, [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5400978"] observed significantly increased levels of BUN in males (≥250 mg/kg-day). This increased circulating BUN was not observed in female rats at doses up to 1,000 mg/kg-day. Click to see interactive graphic for other [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-kidney-effects-kris-v3/"] in HAWC.

4.5 HEPATIC EFFECTS

4.5.1 Human Studies

No human studies were available to inform the potential for PFBS exposure to cause hepatic effects.

4.5.2 Animal Studies

Hepatic effects were evaluated in high-confidence short-term and subchronic studies in rats [ADDIN EN.CITE ADDIN EN.CITE.DATA] and in a high-confidence two-generation reproductive study in rats [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1044</RecNum><

IDText>1578545</IDText><DisplayText>(Lieder et al., 2009b)</DisplayText><record><rec-number>1044</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1044</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lieder, P. H.</author><author>York, R. G.</author><author>Hakes, D. C.</author><author>Chang, S. C.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>A two-generation oral gavage reproduction study with potassium perfluorobutanesulfonate (K+PFBS) in Sprague Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>33-45</pages><volume>259</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>19428941</accession-num><label>1578545</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2009.01.027</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2009.01.027</electronic-resource-num><language>English</language></record></Cite></EndNote>]. Endpoints evaluated in these studies include liver weights, histopathological changes, and serum biomarkers of effect (see [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-liver-effects/"]).

Ten days of daily gavage exposure to K^+PFBS significantly increased absolute, relative-to-body, and relative-to-brain weights of liver in adult male and female S-D rats exposed to 1,000 mg/kg-day [ADDIN EN.CITE <EndNote><Cite><Author>3M</Author><Year>2000</Year><RecNum>1257</RecNum><IDText>4289992</IDText><DisplayText>(3M, 2000d)</DisplayText><record><rec-number>1257</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1257</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>3M,</author></authors></contributors><titles><title>A repeated dose range-finding toxicity study of T-7485 in Sprague-Dawley rats</title></titles><dates><year>2000</year></dates><pub-location>St. Paul, MN</pub-location><publisher>3M Pharmaceuticals</publisher><isbn>Study Number: 132-006</isbn><label>4289992</label><urls></urls><language>English</language><modified-date>3M Company</modified-date></record></Cite></EndNote>]. The absolute liver mass of male rats was increased by 36% compared with females (22%). A similar profile of liver-weight alteration in S-D rats was observed following 28 days of exposure wherein absolute and relative liver weights of high-dose (900 mg/kg-day) male rats had increased 25%–30% [ADDIN EN.CITE <EndNote><Cite><Author>3M</Author><Year>2001</Year><RecNum>602</RecNum><IDText>4241246</IDText><DisplayText>(3M, 2001)</DisplayText><record><rec-number>602</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604955602">602</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>3M,</author></authors></contributors><titles><title>A

28-day oral (gavage) toxicity study of T-7485 in Sprague-Dawley rats</title></titles><dates><year>2001</year></dates><pub-location>St. Paul, MN</pub-location><publisher>3M Corporate Toxicology</publisher><isbn>Study Number: 132-007</isbn><label>4241246</label><urls></urls><language>English</language><modified-date>3M Company</modified-date></record></Cite></EndNote>]. Female rats at the same treatment dose did not experience a similar magnitude increase in absolute or relative liver weights (4–6%). In another 28-day study in S-D rats, K^+PFBS exposure significantly increased absolute and relative liver weights in males (≥125 and ≥62.6 mg/kg-day, respectively) and females (≥250 and ≥125 mg/kg-day, respectively) [ADDIN EN.CITE <EndNote><Cite><Author>NTP</Author><Year>2019</Year><RecNum>1223</RecNum><IDText>5400978</IDText><DisplayText>(NTP, 2019)</DisplayText><record><rec-number>1223</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1223</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NTP,</author></authors></contributors><titles><title>NTP technical report on the toxicity studies of perfluoroalkyl sulfonates (perfluorobutane sulfonic acid, perfluorohexane sulfonate potassium salt, and perfluorooctane sulfonic acid) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats</title></titles><dates><year>2019</year></dates><pub-location>Research Triangle Park, NC</pub-location><isbn>Toxicity Report 96</isbn><label>5400978</label><urls><related-urls><url>https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox096_508.pdf</url></related-urls></urls><language>English</language><modified-date>National Toxicology Program</modified-date></record></Cite></EndNote>]. In contrast, the livers of male and female S-D rats exposed to K^+PFBS at doses up to 600 mg/kg-day for 90 days were not significantly changed compared with respective controls [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1043</RecNum><IDText>1578546</IDText><DisplayText>(Lieder et al., 2009a)</DisplayText><record><rec-number>1043</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1043</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lieder, P. H.</author><author>Chang, S. C.</author><author>York, R. G.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>Toxicological evaluation of potassium perfluorobutanesulfonate in a 90-day oral gavage study with Sprague-Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>45-52</pages><volume>255</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>18992301</accession-num><label>1578546</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2008.10.002</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2008.10.002</electronic-resource-num><language>English</language></record></Cite></EndNote>]. In a two-generation reproduction study using the same strain of rat, however, increased absolute and relative liver

weights were observed in male parental rats exposed to doses of K^+PFBS ≥300 mg/kg-day for approximately 70 days [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1044</RecNum><IDText>1578545</IDText><DisplayText>(Lieder et al., 2009b)</DisplayText><record><rec-number>1044</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1044</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lieder, P. H.</author><author>York, R. G.</author><author>Hakes, D. C.</author><author>Chang, S. C.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>A two-generation oral gavage reproduction study with potassium perfluorobutanesulfonate (K+PFBS) in Sprague Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>33-45</pages><volume>259</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>19428941</accession-num><label>1578545</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2009.01.027</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2009.01.027</electronic-resource-num><language>English</language></record></Cite></EndNote>]. In the F_1 adult males, only relative liver weight was significantly increased at the high dose (1,000 mg/kg-day), although terminal BW was significantly decreased in this group compared with control.

Histopathological examination of the livers of S-D rats across three separate gavage studies of increasing K^+PFBS exposure duration [10-day, [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=4289992"]; 28-day, [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=4241246"]; 90-day, [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578546"]] did not reveal any significant dose-dependent alterations or lesions. For example, focal/multifocal hepatic inflammation was observed in 3/10 male and 4/10 female rats of the high-dose group (no incidence at the low or mid dose) compared to 6/10 male and female rats in the control groups [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1043</RecNum><IDText>1578546</IDText><DisplayText>(Lieder et al., 2009a)</DisplayText><record><rec-number>1043</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1043</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lieder, P. H.</author><author>Chang, S. C.</author><author>York, R. G.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>Toxicological evaluation of potassium perfluorobutanesulfonate in a 90-day oral gavage study with Sprague-Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title>

title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>45-52</pages><volume>255</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>18992301</accession-num><label>1578546</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2008.10.002</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2008.10.002</electronic-resource-num><language>English</language></record></Cite></EndNote>]. The [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578545"] two-generation reproduction gavage study did identify increased incidences of hepatocellular hypertrophy in parental and F_1 adult male rats at ≥300 mg/kg-day; however, this effect was absent in female rats at doses of K^+PFBS up to 1,000 mg/kg-day. [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5400978"] identified a significantly increased incidence of hepatocellular hypertrophy in male (≥125 mg/kg-day) and female (≥500 mg/kg-day) S-D rats after 28 days of K^+PFBS exposure. Further, significantly increased cytoplasmic alteration of hepatocytes was observed in these rats (male and female at ≥500 mg/kg-day). Hepatic necrosis was also observed but was not significant compared with control and only occurred at the high dose (1,000 mg/kg-day) in both sexes [ADDIN EN.CITE <EndNote><Cite><Author>NTP</Author><Year>2019</Year><RecNum>1223</RecNum><IDText>5400978</IDText><DisplayText>(NTP, 2019)</DisplayText><record><rec-number>1223</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1223</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NTP,</author></authors></contributors><titles><title>NTP technical report on the toxicity studies of perfluoroalkyl sulfonates (perfluorobutane sulfonic acid, perfluorohexane sulfonate potassium salt, and perfluorooctane sulfonic acid) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats</title></titles><dates><year>2019</year></dates><pub-location>Research Triangle Park, NC</pub-location><isbn>Toxicity Report 96</isbn><label>5400978</label><urls><related-urls><url>https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox096_508.pdf</url></related-urls></urls><language>English</language><modified-date>National Toxicology Program</modified-date></record></Cite></EndNote>].

In general, serum biomarkers associated with altered liver function or injury, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST), were not significantly changed in male and female S-D rats across multiple gavage studies of varying exposure durations up to 90 days and at K^+PFBS doses up to 1,000 mg/kg-day [ADDIN EN.CITE ADDIN EN.CITE.DATA]. [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5400978"], however, reported increased serum ALT and AST in male (500 mg/kg-day only) and female (≥250 mg/kg-day for ALT; ≥500 mg/kg-day for AST) rats exposed to K^+PFBS for 28 days. Click to see interactive graphic for [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-liver-effects/"] in HAWC.

4.6 EFFECTS ON LIPIDS OR LIPOPROTEINS

4.6.1 Human Studies

One low-confidence study [ADDIN EN.CITE <EndNote><Cite><Author>Zeng</Author><Year>2015</Year><RecNum>696</RecNum><IDText>2851005</IDText><DisplayText>(Zeng et al., 2015)</DisplayText><record><rec-number>696</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">696</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zeng, X. W.</author><author>Qian, Z.</author><author>Emo, B.</author><author>Vaughn, M.</author><author>Bao, J.</author><author>Qin, X. D.</author><author>Zhu, Y.</author><author>Li, J.</author><author>Lee, Y. L.</author><author>Dong, G. H.</author></authors></contributors><titles><title>Association of polyfluoroalkyl chemical exposure with serum lipids in children</title><secondary-title>Science of the Total Environment</secondary-title><alt-title>Sci Total Environ</alt-title><short-title>Science of the Total Environment</short-title></titles><periodical><full-title>Science of the Total Environment</full-title><abbr-1>Sci Total Environ</abbr-1></periodical><alt-periodical><full-title>Science of the Total Environment</full-title><abbr-1>Sci Total Environ</abbr-1></alt-periodical><pages>364-370</pages><volume>512-513</volume><dates><year>2015</year></dates><isbn>ISSN 0048-9697
EISSN 1879-1026</isbn><accession-num>25638651</accession-num><label>2851005</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.scitotenv.2015.01.042</url></related-urls></urls><electronic-resource-num>10.1016/j.scitotenv.2015.01.042</electronic-resource-num><language>English</language></record></Cite></EndNote>] used the controls from the case-control study of asthma described below [ADDIN EN.CITE <EndNote><Cite><Author>Dong</Author><Year>2013</Year><RecNum>833</RecNum><IDText>1937230</IDText><DisplayText>(Dong et al., 2013a)</DisplayText><record><rec-number>833</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">833</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Dong, G. H.</author><author>Tung, K. Y.</author><author>Tsai, C. H.</author><author>Liu, M. M.</author><author>Wang, D.</author><author>Liu, W.</author><author>Jin, Y. H.</author><author>Hsieh, W. S.</author><author>Lee, Y. L.</author><author>Chen, P. C.</author></authors></contributors><titles><title>Serum polyfluoroalkyl concentrations, asthma outcomes, and immunological markers in a case-control study of Taiwanese children</title><secondary-title>Environmental Health Perspectives</secondary-title><alt-title>Environ Health Perspect</alt-title><short-title>Environmental Health Perspectives</short-title></titles><periodical><full-title>Environmental Health Perspectives</full-title><abbr-1>Environ Health Perspect</abbr-1></periodical><alt-periodical><full-title>Environmental Health Perspectives</full-title><abbr-1>Environ Health Perspect</abbr-1></alt-periodical><pages>507-13, 513e1-8</pages><volume>121</volume><number>4</number><dates><year>2013</year></dates><isbn>ISSN 0091-6765
EISSN 1552-9924</isbn><accession-num>23309686</accession-num><label>1937230</label><urls><related-urls><url>http://dx.doi.org/10.1289/ehp.1205351</url></related-urls></urls><electronic-resource-num>10.1289/ehp.1205351</electronic-resource-

num><language>English</language></record></Cite></EndNote>] and examined the association between PFBS exposure and serum lipids. There was a statistically significant increase in total cholesterol (β: 19.3 mg/dL increase per 1 μg/L increase in PFBS; 95% CI: 0.6−38.0) but when PFBS exposure was analyzed in quartiles, no exposure-response gradient was observed.

In addition, a [HYPERLINK "https://hawcprd.epa.gov/rob/study/100515514/"] birth cohort study in China examined associations with childhood adiposity [ADDIN EN.CITE <EndNote><Cite><Author>Chen</Author><Year>2019</Year><RecNum>764</RecNum><ID Text>5080578</IDText><DisplayText>(Chen et al., 2019)</DisplayText><record><rec-number>764</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">764</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Chen, Q.</author><author>Zhang, X.</author><author>Zhao, Y.</author><author>Lu, W.</author><author>Wu, J.</author><author>Zhao, S.</author><author>Zhang, J.</author><author>Huang, L.</author></authors></contributors><titles><title>Prenatal exposure to perfluorobutanesulfonic acid and childhood adiposity: A prospective birth cohort study in Shanghai, China</title><secondary-title>Chemosphere</secondary-title><alt-title>Chemosphere</alt-title><short-title>Chemosphere</short-title></titles><periodical><full-title>Chemosphere</full-title><abbr-1>Chemosphere</abbr-1></periodical><alt-periodical><full-title>Chemosphere</full-title><abbr-1>Chemosphere</abbr-1></alt-periodical><pages>17-23</pages><volume>226</volume><dates><year>2019</year></dates><isbn>ISSN 0045-6535
EISSN 1879-1298</isbn><accession-num>30908964</accession-num><label>5080578</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.chemosphere.2019.03.095</url></related-urls></urls><electronic-resource-num>10.1016/j.chemosphere.2019.03.095</electronic-resource-num><language>English</language></record></Cite></EndNote>]. PFBS was measured in cord blood samples at birth and several measures of adiposity were collected at age 5 years. There was higher adiposity with higher exposure in girls, with significant exposure-response relationships across tertiles with waist circumference, fat mass, body fat percentage, and waist-to-height ratio. No association with adiposity was observed in boys. It is unlikely that the association in girls can be explained by confounding across the other PFAS measured in this study as the associations were strongest for PFBS, but it is possible that there is other unmeasured confounding.

4.6.2 Animal Studies

Beyond a single medium-confidence mouse study [[ADDIN EN.CITE ADDIN EN.CITE.DATA]; summarized below], PFBS studies have not particularly focused on perturbations in lipids or lipoproteins as a potential health outcome, because studies have typically focused only on measures of serum cholesterol and triglyceride as part of a broader panel of clinical chemistry measures in high- or medium-confidence rat studies of 10, 28, and 90 days (see [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-lipid-effects/"]) [[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=4289992"], [HYPERLINK

"https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=4241246"], and [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578546"], respectively]. Circulating levels of cholesterol and triglycerides were unchanged in male and female S-D rats following daily gavage exposure to K^+PFBS for 10 days at doses up to 1,000 mg/kg-day [ADDIN EN.CITE <EndNote><Cite><Author>3M</Author><Year>2000</Year><RecNum>1257</RecNum><IDText>4289992</IDText><DisplayText>(3M, 2000d)</DisplayText><record><rec-number>1257</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1257</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>3M,</author></authors></contributors><titles><title>A repeated dose range-finding toxicity study of T-7485 in Sprague-Dawley rats</title></titles><dates><year>2000</year></dates><pub-location>St. Paul, MN</pub-location><publisher>3M Pharmaceuticals</publisher><isbn>Study Number: 132-006</isbn><label>4289992</label><urls></urls><language>English</language><modified-date>3M Company</modified-date></record></Cite></EndNote>]. In a similarly designed study from the same laboratory, serum cholesterol and triglyceride levels were decreased in male rats but at the high dose only, and this effect was neither statistically significant compared with control nor observed in female rats of the same dose group [ADDIN EN.CITE <EndNote><Cite><Author>3M</Author><Year>2001</Year><RecNum>602</RecNum><IDText>4241246</IDText><DisplayText>(3M, 2001)</DisplayText><record><rec-number>602</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604955602">602</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>3M,</author></authors></contributors><titles><title>A 28-day oral (gavage) toxicity study of T-7485 in Sprague-Dawley rats</title></titles><dates><year>2001</year></dates><pub-location>St. Paul, MN</pub-location><publisher>3M Corporate Toxicology</publisher><isbn>Study Number: 132-007</isbn><label>4241246</label><urls></urls><language>English</language><modified-date>3M Company</modified-date></record></Cite></EndNote>]. Following exposure for up to 90 days, cholesterol and triglycerides were unchanged in male and female rats at doses up to 600 mg/kg-day [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1043</RecNum><IDText>1578546</IDText><DisplayText>(Lieder et al., 2009a)</DisplayText><record><rec-number>1043</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1043</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lieder, P. H.</author><author>Chang, S. C.</author><author>York, R. G.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>Toxicological evaluation of potassium perfluorobutanesulfonate in a 90-day oral gavage study with Sprague-Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>45-

52</pages><volume>255</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>18992301</accession-num><label>1578546</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2008.10.002</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2008.10.002</electronic-resource-num><language>English</language></record></Cite></EndNote>]. PFBS was included in a multi-PFAS study specifically designed to interrogate the mechanism of effect on lipid and lipoprotein metabolism in a transgenic mouse line (APOE*3-Leiden CETP) that is highly responsive to fat and cholesterol intake, consistent with human populations exposed to a western-type diet (containing 14% beef tallow, 1% corn oil, and 0.25% cholesterol) [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Adult male mice were fed a western-type, high-fat diet for 4 weeks prior to initiation of PFBS exposure and throughout the 4- to 6-week PFBS exposure period (at approximately 30 mg/kg-day). This study included several measures of lipid and lipoprotein synthesis, modification, and transport or clearance, such as circulating plasma levels, in vivo clearance of very low-density lipoprotein (VLDL)-like particles, fecal bile acid and sterol excretion, hepatic lipid levels, lipase activity, VLDL-triglyceride and VLDL-apoB production, and gene expression profiles. After 4 weeks of PFBS exposure, fasting plasma triglycerides, cholesteryl ester transfer protein, and glycerol were significantly decreased compared with mice on the control diet. Further, the half-life of VLDL-like particles and hepatic lipase activity, and hepatic cholesteryl ester and free cholesterol levels were decreased [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Hepatic uptake of VLDL-like particles (represents fatty acid/lipid transport into hepatic tissue) was modestly, but significantly, increased compared with control mice. This increased hepatic lipid uptake in the liver was accompanied by increased expression of genes associated with lipid binding, activation, and metabolism (e.g., β-oxidation).

4.7 OTHER EFFECTS

4.7.1 Human Studies

Two studies in China examined different immune outcomes in children [ADDIN EN.CITE ADDIN EN.CITE.DATA].

One [HYPERLINK "https://hawcprd.epa.gov/rob/study/100000894/"] study reported in five publications [ADDIN EN.CITE ADDIN EN.CITE.DATA] examined the association between PFBS exposure and asthma, asthma symptoms, pulmonary function, and related immune markers (immunoglobulin E [IgE], absolute eosinophil count [AEC], eosinophilic cationic protein [ECP], T-helper cell-specific cytokines, and 16-kDa club cell secretory protein). The primary finding was a statistically significant (in the fourth quartile) positive association between incident asthma (i.e., diagnosis in the previous year) and PFBS exposure (OR for Q2: 1.3, 95% CI: 0.7−2.3; OR for Q3: 1.2, 95% CI: 0.7−2.2; OR for Q4: 1.9, 95% CI: 1.1−3.4). There were also increases in AEC and ECP with increased exposure (not statistically significant with the exception of AEC in children with asthma). There was no clear association with IgE or T-helper cell-specific cytokines. There was also no clear association with asthma severity or control of asthma symptoms [ADDIN EN.CITE <EndNote><Cite><Author>Dong</Author><Year>2013</Year><RecNum>833</RecNum><IDText>1937230</IDText><DisplayText>(Dong et al., 2013a)</DisplayText><record><rec-number>833</rec-number><foreign-keys><key app="EN" db-

id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">833</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Dong, G. H.</author><author>Tung, K. Y.</author><author>Tsai, C. H.</author><author>Liu, M. M.</author><author>Wang, D.</author><author>Liu, W.</author><author>Jin, Y. H.</author><author>Hsieh, W. S.</author><author>Lee, Y. L.</author><author>Chen, P. C.</author></authors></contributors><titles><title>Serum polyfluoroalkyl concentrations, asthma outcomes, and immunological markers in a case-control study of Taiwanese children</title><secondary-title>Environmental Health Perspectives</secondary-title><alt-title>Environ Health Perspect</alt-title><short-title>Environmental Health Perspectives</short-title></titles><periodical><full-title>Environmental Health Perspectives</full-title><abbr-1>Environ Health Perspect</abbr-1></periodical><alt-periodical><full-title>Environmental Health Perspectives</full-title><abbr-1>Environ Health Perspect</abbr-1></alt-periodical><pages>507-13, 513e1-8</pages><volume>121</volume><number>4</number><dates><year>2013</year></dates><isbn>ISSN 0091-6765
EISSN 1552-9924</isbn><accession-num>23309686</accession-num><label>1937230</label><urls><related-urls><url>http://dx.doi.org/10.1289/ehp.1205351</url></related-urls></urls><electronic-resource-num>10.1289/ehp.1205351</electronic-resource-num><language>English</language></record></Cite></EndNote>], or pulmonary function measured with spirometry among children with asthma [ADDIN EN.CITE <EndNote><Cite><Author>Qin</Author><Year>2017</Year><RecNum>872</RecNum><IDText>3869265</IDText><DisplayText>(Qin et al., 2017)</DisplayText><record><rec-number>872</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">872</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Qin, X. D.</author><author>Qian, Z. M.</author><author>Dharmage, S. C.</author><author>Perret, J.</author><author>Geiger, S. D.</author><author>Rigdon, S. E.</author><author>Howard, S.
author><author>Zeng, X. W.</author><author>Hu, L. W.</author><author>Yang, B. Y.</author><author>Zhou, Y.</author><author>Li, M.</author><author>Xu, S. L.</author><author>Bao, W. W.</author><author>Zhang, Y. Z.</author><author>Yuan, P.</author><author>Wang, J.</author><author>Zhang, C.</author><author>Tian, Y. P.</author><author>Nian, M.</author><author>Xiao, X.</author><author>Chen, W.</author><author>Lee, Y. L.</author><author>Dong, G. H.</author></authors></contributors><titles><title>Association of perfluoroalkyl substances exposure with impaired lung function in children</title><secondary-title>Environmental Research</secondary-title><alt-title>Environ Res</alt-title><short-title>Environmental Research</short-title></titles><periodical><full-title>Environmental Research</full-title><abbr-1>Environ Res</abbr-1></periodical><alt-periodical><full-title>Environmental Research</full-title><abbr-1>Environ Res</abbr-1></alt-periodical><pages>15-21</pages><volume>155</volume><dates><year>2017</year></dates><isbn>ISSN 0013-9351
EISSN 1096-0953</isbn><accession-num>28171771</accession-num><label>3869265</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.envres.2017.01.025</url></related-urls></urls><electronic-resource-num>10.1016/j.envres.2017.01.025</electronic-resource-num><language>English</language></record></Cite></EndNote>]. While reduced pulmonary function could be considered an outcome separate from asthma, the study authors noted no

associations in pulmonary function (i.e., in nonasthmatics across the PFAS they studied), so for these purposes, it was considered an indicator of asthma severity.

One [HYPERLINK "https://hawcprd.epa.gov/rob/study/100001480/"] study [ADDIN EN.CITE <EndNote><Cite><Author>Chen</Author><Year>2018</Year><RecNum>1189</RecNum><IDText>4238372</IDText><DisplayText>(Chen et al., 2018)</DisplayText><record><rec-number>1189</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1189</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Chen, Q.</author><author>Huang, R.</author><author>Hua, L.</author><author>Guo, Y.</author><author>Huang, L.</author><author>Zhao, Y.</author><author>Wang, X.</author><author>Zhang, J.</author></authors></contributors><titles><title>Prenatal exposure to perfluoroalkyl and polyfluoroalkyl substances and childhood atopic dermatitis: A prospective birth cohort study</title><secondary-title>Environmental Health: A Global Access Science Source</secondary-title><alt-title>Environ Health</alt-title><short-title>Environmental Health: A Global Access Science Source</short-title></titles><periodical><full-title>Environmental Health: A Global Access Science Source</full-title><abbr-1>Environ Health</abbr-1></periodical><alt-periodical><full-title>Environmental Health: A Global Access Science Source</full-title><abbr-1>Environ Health</abbr-1></alt-periodical><pages>1-12</pages><volume>17</volume><number>1</number><dates><year>2018</year></dates><isbn>ISSN 1476-069X
EISSN 1476-069X</isbn><accession-num>29343261</accession-num><label>4238372</label><urls><related-urls><url>http://dx.doi.org/10.1186/s12940-018-0352-7</url></related-urls></urls><electronic-resource-num>10.1186/s12940-018-0352-7</electronic-resource-num><language>English</language></record></Cite></EndNote>] examined the association between PFBS exposure and atopic dermatitis and reported a statistically nonsignificant increase in atopic dermatitis with increased exposure (OR: 1.23; 95% CI: 0.74−2.04).

In addition, two studies examined cardiovascular effects [ADDIN EN.CITE ADDIN EN.CITE.DATA], but it is difficult to evaluate consistency across studies given the different outcomes in each.

One [HYPERLINK "https://hawcprd.epa.gov/rob/study/100515512/"] study [ADDIN EN.CITE <EndNote><Cite><Author>Huang</Author><Year>2018</Year><RecNum>290</RecNum><IDText>5024212</IDText><DisplayText>(Huang et al., 2018)</DisplayText><record><rec-number>290</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604955453">290</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Huang, M.</author><author>Jiao, J.</author><author>Zhuang, P.</author><author>Chen, X.</author><author>Wang, J.</author><author>Zhang, Y.</author></authors></contributors><titles><title>Serum polyfluoroalkyl chemicals are associated with risk of cardiovascular diseases in national US population</title><secondary-title>Environment International</secondary-title><alt-title>Environ Int</alt-title><short-title>Environment International</short-title></titles><periodical><full-title>Environment

International</full-title><abbr-1>Environ Int</abbr-1></periodical><alt-periodical><full-title>Environment International</full-title><abbr-1>Environ Int</abbr-1></alt-periodical><pages>37-46</pages><volume>119</volume><number>Elsevier</number><dates><year>2018</year></dates><isbn>ISSN 0160-4120
EISSN 1873-6750</isbn><accession-num>29933236</accession-num><label>5024212</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.envint.2018.05.051</url></related-urls></urls><electronic-resource-num>10.1016/j.envint.2018.05.051</electronic-resource-num><language>English</language></record></Cite></EndNote>] using data from NHANES cycles for 1999–2014 reported significantly higher odds of total cardiovascular disease with higher exposure (OR for above vs. below the LOD: 1.19; 95% CI: 1.06–1.32) and elevated, though not statistically significant, odds of individual types of cardiovascular disease (congestive heart failure, coronary heart disease, angina pectoris, heart attack, and stroke). There is potential in this study for confounding across the PFAS, because PFBS was highly correlated with some other PFAS with slightly stronger associations.

A [HYPERLINK "https://hawcprd.epa.gov/rob/study/100515515/"] cross-sectional study [ADDIN EN.CITE <EndNote><Cite><Author>Huang</Author><Year>2019</Year><RecNum>1188</RecNum><IDText>5083564</IDText><DisplayText>(Huang et al., 2019b)</DisplayText><record><rec-number>1188</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1188</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Huang, R.</author><author>Chen, Q.</author><author>Zhang, L.</author><author>Luo, K.</author><author>Chen, L.</author><author>Zhao, S.</author><author>Feng, L.</author><author>Zhang, J.</author></authors></contributors><titles><title>Prenatal exposure to perfluoroalkyl and polyfluoroalkyl substances and the risk of hypertensive disorders of pregnancy</title><secondary-title>Environmental Health: A Global Access Science Source</secondary-title><alt-title>Environ Health</alt-title><short-title>Environmental Health: A Global Access Science Source</short-title></titles><periodical><full-title>Environmental Health: A Global Access Science Source</full-title><abbr-1>Environ Health</abbr-1></periodical><alt-periodical><full-title>Environmental Health: A Global Access Science Source</full-title><abbr-1>Environ Health</abbr-1></alt-periodical><pages>5</pages><volume>18</volume><number>1</number><dates><year>2019</year></dates><isbn>ISSN 1476-069X
EISSN 1476-069X</isbn><accession-num>30626391</accession-num><label>5083564</label><urls><related-urls><url>http://dx.doi.org/10.1186/s12940-018-0445-3</url></related-urls></urls><electronic-resource-num>10.1186/s12940-018-0445-3</electronic-resource-num><language>English</language></record></Cite></EndNote>] of hypertensive disorders of pregnancy reported higher odds for all such disorders in pregnancy (in the third tertile) (OR for Tertile 2 vs. Tertile 1: 0.89, 95% CI: 0.39–2.44; OR for Tertile 3: 2.26, 95% CI: 1.02–5.0; *p*-trend 0.03) and pre-eclampsia (OR for Tertile 2 vs. Tertile 1: 2.09, 95% CI: 0.51–8.53; OR for Tertile 3: 3.51, 95% CI: 0.94–13.2; *p*-trend 0.05), with both trends being statistically significant after mutual adjustment of PFAS.

4.7.2 Animal Studies

Other effects were evaluated following exposure to PFBS, including outcomes related to the spleen, hematological system, BW, neurotoxicity, and nonspecific clinical chemistry. These groups of outcomes were not synthesized because of inadequate available information, uncertain biological relevance, and/or inconsistencies across studies and sexes.

4.8 OTHER DATA

Other studies that used PFBS or K^+PFBS are described in this section. These studies are not adequate for determining RfD values and were considered supportive data. These data might include acute-duration exposures, genotoxicity, mechanistic, and other studies (see [REF _Ref288392097 \h]).

ED_006316_00006861-00113

Table [SEQ Table * ARABIC]. Other Studies				
Test	**Materials and Methods**	**Results**	**Conclusions**	**References**
Genotoxicity				
Mutagenicity test	*Salmonella typhimurium* (strains TA98 and TA100) and *Escherichia coli* (strain pKM101) in the presence or absence of S9. Concentrations of PFBS were between 0−5,000 µg/plate.	Test was negative for TA100 and pKM101 strains and equivocal for TA98 strain.	There is no in vitro evidence of PFBS mutagenicity.	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1784743"]
Ames	*S. typhimurium* (strains TA98, TA100, TA1535, and TA1537) and *E. coli* (strain WP2uvrA) were tested in the presence or absence of S9 and with or without a preincubation treatment. Concentrations of K^+PFBS were between 0−5,000 µg/plate.	The results of both mutation assays indicate that PFBS did not induce any significant increase in the number of revertant colonies for any of the tester strains in the presence or absence of induced rat liver S9.	There is no in vitro evidence of PFBS mutagenicity.	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=4322455"]
Genotoxicity test	Human hepatoma (HepG2) cells were treated with 0.4 µM to 2 mM PFBS. Intracellular ROS production was measured by use of 2′,7′-dichlorofluorescein diacetate and DNA damage was measured with the comet assay.	The amount of ROS and DNA strand breaks remained unaffected by PFBS treatment.	PFBS did not generate ROS or DNA damage in human liver cells.	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578507"]
CHO chromosomal aberration	Cultures of CHO cells were treated with K^+PFBS at concentrations ranging from 0 to 5,000 µg/mL with or without exogenous metabolic activation. The in vitro exposure duration was 3 hr.	PFBS did not induce a statistically significant increase in the percentage of cells with aberrations at any of the concentrations tested, either with or without metabolic activation, in either assay when compared to the solvent controls.	Based on the negative results in the in vitro CA assay in CHO cells, PFBS is not considered to be a clastogenic agent.	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=4322456"]

Table [SEQ Table * ARABIC]. Other Studies				
Test	**Materials and Methods**	**Results**	**Conclusions**	**References**
Micronucleus assay	Male and female S-D rats (5/group) were exposed twice daily to K^+PFBS by gavage at doses of 31.3, 62.5, 125, or 250 mg/kg for 28 d.	PFBS did not induce a statistically significant increase in the frequency of micronucleated polychromatic erythrocytes.	PFBS was negative for micronuclei in the blood of male and female rats, indicating a lack of genotoxic potential.	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3860004"]
Acute duration and other routes of exposure				
Acute	10 rats/group, young adult male rat (strain not specified), administered PFBS by gavage, single dose, 50, 100, 300, 600, or 800 µL/kg and observed for 14 d postexposure.	Mortality: 0, 20, 60, 80, and 100% at 50, 100, 300, 600, and 800 µL/kg PFBS, respectively.	Acute oral PFBS rat LD_{50} in male rats is 236 µL/kg (corresponding to 430 mg/kg).	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3859928"] [HYPERLINK "https://hawcprd.epa.gov/rob/study/100000969/"]
Acute dermal	Adult (8 wk of age) male and female S-D rats (5/group) were exposed dermally (10% of body surface area) to 500, 1,000, or 2,000 mg/kg K^+PFBS for 24 hr and then observed for 15 d postexposure for signs of clinical toxicity, mortality, BW changes, or gross pathology (terminus of study).	No treatment-related observations were noted.	PFBS is not acutely toxic via the dermal route of exposure in rats.	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=4322450"]
Dermal irritation	Adult (14-wk of age) female NZW rabbits (3 rabbits total for study) were exposed dermally (6 cm^2 of skin) to 500 mg K^+PFBS for approximately 4 hr and then observed for 9 d postexposure for signs of clinical toxicity, mortality, or BW changes.	Draize scoring was performed on the patch site immediately following the exposure period and 24, 48, and 72 hr postexposure. No signs of dermal irritation were observed. No signs of clinical toxicity or mortality occurred. No treatment-related alterations in BW were noted.	PFBS did not induce erythema, edema, or other possible dermal findings during the scoring periods, indicating a lack of dermal irritant properties in rabbits.	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=4322452"]

Table [SEQ Table * ARABIC]. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Ocular sensitivity	Adult (16-wk of age) female NZW rabbits (3 rabbits total for study) were exposed to approximately 80 mg K^+PFBS via ocular installation in the left eye for 2 sec. Eyes were flushed with 0.9% saline after 24 hr and then observed and scored for up to 21 d postexposure. The rabbits were also followed for clinical signs of toxicity or mortality/moribundity.	Excessive lacrimation of the left eyes noted throughout study postexposure. Based on the laboratory scoring system, PFBS was "moderately" irritating at 24 and 72 hr postexposure.	PFBS is a moderate ocular irritant in rabbits.	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=4322453"]
Contact hypersensitivity	Adult male (10−12 wk old) and female (9 wk old) CRL:(HA)BR Hartley guinea pigs were injected intradermally with sterile water, Freund's adjuvant, or adjuvant containing 125 mg/mL K^+PFBS (induction phase). D 7 after induction, a petrolatum paste containing 0.5 g K^+PFBS was applied to the previous injection site of the guinea pigs for 48 hr (topical induction phase). D 22, a challenge dose of 0.5 g K^+PFBS (petrolatum paste) was applied to the shaved left cranial flank (right flanks were treated with petrolatum paste only) (challenge phase). This challenge procedure was repeated on D 29. Challenge sites were observed and scored following each challenge period (D 24−25 males and females and D 31−32 males only). Guinea pigs were also followed for signs of clinical toxicity, mortality/moribundity, or alterations in BW.	No mortalities, clinical signs of toxicity, or changes in BW associated with PFBS exposure were noted. Dermal scores were zero (no response) in females and did not exceed 1 in males (discreet or patchy edema), which was not considered significant compared with control guinea pigs exposed to Freund's adjuvant alone.	PFBS is not considered an allergen in the guinea pig maximization test.	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=4322454"]

BW = body weight; CA = chromosomal aberration; CHO = Chinese hamster ovary; DNA = deoxyribonucleic acid; K^+PFBS = potassium perfluorobutane sulfonate; LD_{50} = median lethal dose; NZW = New Zealand White; PFBS = perfluorobutane sulfonic acid; ROS = reactive oxygen species; S-D = Sprague-Dawley.

4.8.1 Tests Evaluating Genotoxicity and Mutagenicity

Genotoxic, mutagenic, and clastogenic effects of PFBS have been tested in mammalian and prokaryotic cells in vitro [ADDIN EN.CITE ADDIN EN.CITE.DATA], and in rats in vivo [ADDIN EN.CITE <EndNote><Cite><Author>NTP</Author><Year>2019</Year><RecNum>1223</RecNum><IDText>5400978</IDText><DisplayText>(NTP, 2019)</DisplayText><record><rec-number>1223</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1223</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NTP,</author></authors></contributors><titles><title>NTP technical report on the toxicity studies of perfluoroalkyl sulfonates (perfluorobutane sulfonic acid, perfluorohexane sulfonate potassium salt, and perfluorooctane sulfonic acid) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats</title></titles><dates><year>2019</year></dates><pub-location>Research Triangle Park, NC</pub-location><isbn>Toxicity Report 96</isbn><label>5400978</label><urls><related-urls><url>https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox096_508.pdf</url></related-urls></urls><language>English</language><modified-date>National Toxicology Program</modified-date></record></Cite></EndNote>]. PFBS was negative for mutagenicity in *Escherichia coli* strain pKM101 and *Salmonella typhimurium* strain TA100 [ADDIN EN.CITE <EndNote><Cite><Author>NTP</Author><Year>2005</Year><RecNum>1305</RecNum><IDText>1784743</IDText><DisplayText>(NTP, 2005)</DisplayText><record><rec-number>1305</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1305</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NTP,</author></authors></contributors><titles><title>Perfluorobutane sulfonate. Genetic toxicology - bacterial mutagenicity. Chemical effects in biological systems (CEBS)</title></titles><dates><year>2005</year></dates><pub-location>Research Triangle Park, NC</pub-location><publisher>National Institutes of Environmental Sciences, National Institutes of Health</publisher><isbn>Study ID A32037</isbn><label>1784743</label><urls><related-urls><url>http://tools.niehs.nih.gov/cebs3/ntpViews/?activeTab=detail&studyNumber=A32037</url></related-urls></urls><language>English</language><modified-date>National Toxicology Program</modified-date></record></Cite></EndNote>]. Mutagenicity test results were equivocal in *S. typhimurium* strain TA98. [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=4322455"] tested PFBS at concentrations up to 5,000 µg/plate in *E. coli* strain WP2uvrA and *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 in the presence or absence of exogenous metabolic activation and found no evidence of mutagenic activity. In mammalian cells in vitro, PFBS did not generate reactive oxygen species (ROS) or oxidative deoxyribonucleic acid damage in HepG2 cells [ADDIN EN.CITE <EndNote><Cite><Author>Eriksen</Author><Year>2010</Year><RecNum>733</RecNum><IDText>1578507</IDText><DisplayText>(Eriksen et al., 2010)</DisplayText><record><rec-number>733</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">733</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>Eriksen, K. T.</author><author>Raaschou-Nielsen, O.</author><author>Sørensen, M.</author><author>Roursgaard, M.</author><author>Loft, S.</author><author>Møller, P.</author></authors></contributors><titles><title>Genotoxic potential of the perfluorinated chemicals PFOA, PFOS, PFBS, PFNA and PFHxA in human HepG2 cells</title><secondary-title>Mutation Research</secondary-title><alt-title>Mutat Res</alt-title><short-title>Mutation Research</short-title></titles><periodical><full-title>Mutation Research</full-title><abbr-1>Mutat Res</abbr-1></periodical><alt-periodical><full-title>Mutation Research</full-title><abbr-1>Mutat Res</abbr-1></alt-periodical><pages>39-43</pages><volume>700</volume><number>1-2</number><dates><year>2010</year></dates><isbn>ISSN 0027-5107
EISSN 1873-135X</isbn><accession-num>20451658</accession-num><label>1578507</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.mrgentox.2010.04.024</url></related-urls></urls><electronic-resource-num>10.1016/j.mrgentox.2010.04.024</electronic-resource-num><language>English</language></record></Cite></EndNote>]. PFBS also failed to induce chromosomal aberrations in Chinese hamster ovary cells, suggesting a lack of clastogenic activity [ADDIN EN.CITE <EndNote><Cite><Author>Xu</Author><Year>2001</Year><RecNum>1249</RecNum><IDText>4322456</IDText><DisplayText>(Xu, 2001)</DisplayText><record><rec-number>1249</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1249</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>Xu, J.</author></authors></contributors><titles><title>Test for chemical induction of chromosome aberration in cultured Chinese hamster ovary (CHO) cells with and without metabolic activation</title></titles><dates><year>2001</year></dates><pub-location>Redfield, AR</pub-location><publisher>Primedica Redfield</publisher><isbn>Sponsor's study no. 132-009</isbn><label>4322456</label><urls></urls><language>English</language></record></Cite></EndNote>]. Adult male and female S-D rats exposed twice daily to oral PFBS at doses up to 250 mg/kg for 28 days did not experience any significant increases in micronucleated polychromatic erythrocytes, indicating a lack of genotoxic activity (see [REF _Ref288392097 \h]) [ADDIN EN.CITE <EndNote><Cite><Author>NTP</Author><Year>2012</Year><RecNum>1281</RecNum><IDText>3860004</IDText><DisplayText>(NTP, 2012)</DisplayText><record><rec-number>1281</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1281</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NTP,</author></authors></contributors><titles><title>Perfluorobutane sulfonate. Genetic toxicology - micronucleus</title></titles><dates><year>2012</year></dates><pub-location>Research Triangle Park, NC</pub-location><publisher>U.S. Department of Health and Human Services, National Institutes of Environmental Sciences, National Institutes of Health</publisher><label>3860004</label><work-type>NTP</work-type><urls><related-urls><url>https://tools.niehs.nih.gov/cebs3/ntpViews/?studyNumber=002-01134-0002-0000-3</url></related-urls></urls><language>English</language><modified-date>National Toxicology Program</modified-date></record></Cite></EndNote>].

4.8.2 Acute Duration and Other Routes of Exposure

Limited data are available to evaluate acute toxicity and effects from dermal exposure to PFBS (see [REF _Ref288392097 \h]). One low-confidence acute oral toxicity study on male rats administered PFBS by gavage reported a median lethal dose (LD_{50}) of 236 μL/kg (corresponding to 430 mg/kg) [ADDIN EN.CITE <EndNote><Cite><Author>Bomhard</Author><Year>1996</Year><RecNum>1177</RecNum><IDText>3859928</IDText><DisplayText>(Bomhard and Löser, 1996)</DisplayText><record><rec-number>1177</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1177</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bomhard, E.</author><author>Löser, E.</author></authors></contributors><titles><title>Acute toxicologic evaluation of perfluorobutanesulfonic acid</title><secondary-title>Journal of the American College of Toxicology, Part B: Acute Toxicity Data</secondary-title><alt-title>J Am Coll Toxicol B Acute Toxic Data</alt-title><short-title>Journal of the American College of Toxicology, Part B: Acute Toxicity Data</short-title></titles><periodical><full-title>Journal of the American College of Toxicology, Part B: Acute Toxicity Data</full-title><abbr-1>J Am Coll Toxicol B Acute Toxic Data</abbr-1></periodical><alt-periodical><full-title>Journal of the American College of Toxicology, Part B: Acute Toxicity Data</full-title><abbr-1>J Am Coll Toxicol B Acute Toxic Data</abbr-1></alt-periodical><pages>S105</pages><volume>15</volume><number>Suppl. 1</number><dates><year>1996</year></dates><isbn>ISSN 1044-2049</isbn><label>3859928</label><urls><related-urls><url>http://dx.doi.org/10.1177/10915818960150S175</url></related-urls></urls><electronic-resource-num>10.1177/10915818960150s175</electronic-resource-num><language>English</language></record></Cite></EndNote>]. One acute dermal toxicity study concluded that PFBS is not acutely toxic via the dermal route of exposure in rats, with no treatment-related observation at doses up to 2,000 mg/kg [ADDIN EN.CITE <EndNote><Cite><Author>3M</Author><Year>2000</Year><RecNum>1254</RecNum><IDText>4322450</IDText><DisplayText>(3M, 2000b)</DisplayText><record><rec-number>1254</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1254</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>3M,</author></authors></contributors><titles><title>Acute dermal toxicity study of T-7485 applied to Sprague-Dawley rats</title></titles><dates><year>2000</year></dates><pub-location>St. Paul, MN</pub-location><publisher>3M Corporate Toxicology</publisher><isbn>Study Number: 132-010</isbn><label>4322450</label><urls></urls><language>English</language><modified-date>3M Company</modified-date></record></Cite></EndNote>]. PFBS was not reported to induce erythema, edema, or other possible dermal findings during the scoring periods, indicating a lack of dermal irritant properties in rabbits exposed to 500 mg K^+PFBS for approximately 4 hours [ADDIN EN.CITE <EndNote><Cite><Author>3M</Author><Year>2000</Year><RecNum>1253</RecNum><IDText>4322452</IDText><DisplayText>(3M, 2000a)</DisplayText><record><rec-number>1253</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1253</key></foreign-keys><ref-type name="Report">27</ref-type>

type><contributors><authors><author>3M,</author></authors></contributors><titles><title>A cute dermal irritation study of T-7485 applied to New Zealand white rabbits</title></titles><dates><year>2000</year></dates><pub-location>St. Paul, MN</pub-location><publisher>3M Corporate Toxicology</publisher><isbn>Study Number: 132-004</isbn><label>4322452</label><urls></urls><language>English</language><modified-date>3M Company</modified-date></record></Cite></EndNote>]. PFBS was found to be a moderate ocular irritant in rabbits exposed to 80 mg K^+PFBS via ocular installation [ADDIN EN.CITE <EndNote><Cite><Author>3M</Author><Year>2000</Year><RecNum>1252</RecNum><IDText>4322453</IDText><DisplayText>(3M, 2000c)</DisplayText><record><rec-number>1252</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1252</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>3M,</author></authors></contributors><titles><title>A cute ocular irritation study of T-7485 applied to New Zealand white rabbits</title></titles><dates><year>2000</year></dates><pub-location>St. Paul, MN</pub-location><publisher>3M Corporate Toxicology</publisher><isbn>Study Number: 132-005</isbn><label>4322453</label><urls></urls><language>English</language><modified-date>3M Company</modified-date></record></Cite></EndNote>]. PFBS did not induce skin sensitization in the guinea pig maximization test with an intradermal injection of 125 mg/mL and topical induction of 0.5 g K^+PFBS [ADDIN EN.CITE <EndNote><Cite><Author>3M</Author><Year>2002</Year><RecNum>1251</RecNum><IDText>4322454</IDText><DisplayText>(3M, 2002a)</DisplayText><record><rec-number>1251</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1251</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>3M,</author></authors></contributors><titles><title>D elayed contact hypersensitivity study of T-7485 in Hartley guinea pigs (maximization test)</title></titles><dates><year>2002</year></dates><pub-location>St. Paul, MN</pub-location><publisher>3M Corporate Toxicology</publisher><isbn>Study Number: 132-015</isbn><label>4322454</label><urls></urls><language>English</language><modified-date>3M Company</modified-date></record></Cite></EndNote>].

5.0 EVIDENCE INTEGRATION AND HAZARD CHARACTERIZATION

The epidemiology database of studies of PFBS exposure and health effects consists of 19 epidemiologic studies (described in 22 publications), summarized in the previous section. The experimental animal database of all repeated-dose oral toxicity studies for PFBS and the related compound K^+PFBS includes a short-term range-finding study in rats [ADDIN EN.CITE <EndNote><Cite><Author>3M</Author><Year>2000</Year><RecNum>1257</RecNum><IDText>4289992</IDText><DisplayText>(3M, 2000d)</DisplayText><record><rec-number>1257</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1257</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>3M,</author></authors></contributors><titles><title>A repeated dose range-finding toxicity study of T-7485 in Sprague-Dawley rats</title></titles><dates><year>2000</year></dates><pub-location>St. Paul, MN</pub-location><publisher>3M Pharmaceuticals</publisher><isbn>Study Number: 132-006</isbn><label>4289992</label><urls></urls><language>English</language><modified-date>3M Company</modified-date></record></Cite></EndNote>], two 28-day studies in rats [ADDIN EN.CITE <EndNote><Cite><Author>3M</Author><Year>2001</Year><RecNum>602</RecNum><IDText>4241246</IDText><DisplayText>(NTP, 2019; 3M, 2001)</DisplayText><record><rec-number>602</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604955602">602</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>3M,</author></authors></contributors><titles><title>A 28-day oral (gavage) toxicity study of T-7485 in Sprague-Dawley rats</title></titles><dates><year>2001</year></dates><pub-location>St. Paul, MN</pub-location><publisher>3M Corporate Toxicology</publisher><isbn>Study Number: 132-007</isbn><label>4241246</label><urls></urls><language>English</language><modified-date>3M Company</modified-date></record></Cite><Cite><Author>NTP</Author><Year>2019</Year><RecNum>1223</RecNum><IDText>5400978</IDText><record><rec-number>1223</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1223</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NTP,</author></authors></contributors><titles><title>NTP technical report on the toxicity studies of perfluoroalkyl sulfonates (perfluorobutane sulfonic acid, perfluorohexane sulfonate potassium salt, and perfluorooctane sulfonic acid) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats</title></titles><dates><year>2019</year></dates><pub-location>Research Triangle Park, NC</pub-location><isbn>Toxicity Report 96</isbn><label>5400978</label><urls><related-urls><url>https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox096_508.pdf</url></related-urls></urls><language>English</language><modified-date>National Toxicology Program</modified-date></record></Cite></EndNote>], one subchronic study in rats [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1043</RecNum><IDText>1578546</IDText><DisplayText>(Lieder et al., 2009a)</DisplayText><record><rec-number>1043</rec-number><foreign-keys><key app="EN" db-

id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1043</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lieder, P. H.</author><author>Chang, S. C.</author><author>York, R. G.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>Toxicological evaluation of potassium perfluorobutanesulfonate in a 90-day oral gavage study with Sprague-Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>45-52</pages><volume>255</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>18992301</accession-num><label>1578546</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2008.10.002</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2008.10.002</electronic-resource-num><language>English</language></record></Cite></EndNote>], one subchronic-duration lipoprotein metabolism study in mice [ADDIN EN.CITE ADDIN EN.CITE.DATA], three gestational exposure studies in mice and rats [ADDIN EN.CITE ADDIN EN.CITE.DATA], and a two-generation reproductive toxicity study in rats [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1044</RecNum><IDText>1578545</IDText><DisplayText>(Lieder et al., 2009b)</DisplayText><record><rec-number>1044</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1044</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lieder, P. H.</author><author>York, R. G.</author><author>Hakes, D. C.</author><author>Chang, S. C.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>A two-generation oral gavage reproduction study with potassium perfluorobutanesulfonate (K+PFBS) in Sprague Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>33-45</pages><volume>259</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>19428941</accession-num><label>1578545</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2009.01.027</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2009.01.027</electronic-resource-num><language>English</language></record></Cite></EndNote>]. Health outcomes evaluated across available studies included effects on the thyroid, reproductive organs and tissues, developing offspring, kidneys, liver, and lipids/lipoproteins following oral exposure to PFBS. [REF _Ref55818122 \h] provides an overview of this database of potentially relevant studies and effects. This table includes only the high- and medium-confidence animal studies (a single, low-confidence animal study was not considered informative for drawing conclusions on potential health hazard[s]). The available epidemiology studies are also not included because

their ability to inform conclusions about associations was limited because of the small number of studies (typically one) per outcome and poor sensitivity resulting from low exposure levels.

Following the summary of the available database in [REF _Ref55818122 \h], narrative summaries describe the evidence integration judgments and the primary rationales supporting these decisions for each health effect. These narratives are supported by an evidence profile table that succinctly lays out the various factors that were judged to increase or decrease the support for a hazard. While the epidemiology studies were not influential in drawing evidence integration judgments (i.e., they were judged as equivocal for all outcomes) or the derivation of toxicity values (i.e., these studies are not discussed in the next section), the general findings are summarized below to provide context to the animal study findings and identify potential areas of future research.

ED_006316_00006861-00123

Table [SEQ Table * ARABIC]. Summary of Noncancer Data for Oral Exposure to PFBS (CASRN 375-73-5) and the Related Compound K^+PFBS (CASRN 29420-49-3)

Exposure Duration[a]	Reference	Study Confidence	Number of Male/Female, Strain, Species, Study Type, Study Duration	Doses Tested (mg/kg-d)	Effects Observed at LOAEL	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)
Short term	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=4289992"]	[HYPERLINK "https://hawcprd.epa.gov/rob/study/100001452/"]	5/5, S-D rat, K^+PFBS administered by gavage, 10 d	0, 100, 300, 1,000	Increased absolute and relative liver weight.	300	1,000
Short term	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=4241246"]	[HYPERLINK "https://hawcprd.epa.gov/rob/study/100001409/"]	10/10, S-D rat, K^+PFBS administered by gavage, 28 d	0, 100, 300, 900	Increased absolute and relative liver weight (male) and relative kidney weight (female).	300	900

Table [SEQ Table * ARABIC]. Summary of Noncancer Data for Oral Exposure to PFBS (CASRN 375-73-5) and the Related Compound K^+PFBS (CASRN 29420-49-3)

Exposure Duration[a]	Reference	Study Confidence	Number of Male/Female, Strain, Species, Study Type, Study Duration	Doses Tested (mg/kg-d)	Effects Observed at LOAEL	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)
Short term	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5400978"]	[HYPERLINK "https://hawcprd.epa.gov/rob/study/100001456/"]	10/10, S-D rat, PFBS administered by gavage, twice/d, 28 d	0, 62.6, 125, 250, 500, 1,000[b]	Decreased T_3, free T_4, total T_4 in males and females. Increased relative liver weight in females and increased relative right kidney weight in males.	NDr	62.6
Subchronic	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578546"]; [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=4289575"]	[HYPERLINK "https://hawcprd.epa.gov/rob/study/100000964/"]	10/10, S-D rat, K^+PFBS administered by gavage, 7 d/wk, 90 d	0, 60, 200, 600	Increased incidence of renal hyperplasia in males and females.	200	600

Table [SEQ Table * ARABIC]. Summary of Noncancer Data for Oral Exposure to PFBS (CASRN 375-73-5) and the Related Compound K^+PFBS (CASRN 29420-49-3)

Exposure Duration[a]	Reference	Study Confidence	Number of Male/Female, Strain, Species, Study Type, Study Duration	Doses Tested (mg/kg-d)	Effects Observed at LOAEL	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)
Subchronic	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578502"]; [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3927382"]	[HYPERLINK "https://hawcprd.epa.gov/rob/study/100000970/"]	6–8/0, Apoe*3-Leiden CETP mice, K^+PFBS in diet, 4–6 wk	0, 30	Alterations in lipid homeostasis (e.g., decreased hepatic lipase, triglycerides) is of uncertain biological significance.	NDr	NDr

Table [SEQ Table * ARABIC]. Summary of Noncancer Data for Oral Exposure to PFBS (CASRN 375-73-5) and the Related Compound K^+PFBS (CASRN 29420-49-3)

Exposure Duration[a]	Reference	Study Confidence	Number of Male/Female, Strain, Species, Study Type, Study Duration	Doses Tested (mg/kg-d)	Effects Observed at LOAEL	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)
Developmental	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"]	[HYPERLINK "https://hawcprd.epa.gov/rob/study/100000968/"]	0/10, ICR mice, K^+PFBS administered by gavage, GDs 1−20	0, 50, 200, 500	Decreased T_3, free T_4, and total T_4 in dams and PND 1, 30, and 60 offspring. Increased TSH in maternal and offspring (PND 30 only). Delayed eyes opening, vaginal opening, and first estrous and decreased BW in pups.	50	200

Developmental	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=4322522"]	[HYPERLINK "https://hawcprd.epa.gov/rob/study/100001477/"]	0/8, S-D rat, K^+PFBS administered by gavage, GDs 6–20	0, 100, 300, 1,000, 2,000	Decreased maternal feed consumption, BW gain, and gravid uterine weight. Decreased pup BW occurred at doses affecting maternal health, limiting the interpretation of the results; thus, developmental effect levels were not determined. (Limited endpoints evaluated—pilot study.)	P_0: 1,000 F_1: NDr	P_0: 2,000 F_1: NDr
Developmental	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=4289675"]	[HYPERLINK "https://hawcprd.epa.gov/rob/study/100001411/"]	0/25, S-D rat, K^+PFBS administered by gavage, GDs 6–20	0, 100, 300, 1,000	Decreased maternal feed consumption and BW gain. Decreased pup BW occurred at doses	P_0: 300 F_1: NDr	P_0: 1,000 F_1: NDr

Table [SEQ Table * ARABIC]. Summary of Noncancer Data for Oral Exposure to PFBS (CASRN 375-73-5) and the Related Compound K^+PFBS (CASRN 29420-49-3)							
Exposure Duration[a]	**Reference**	**Study Confidence**	**Number of Male/Female, Strain, Species, Study Type, Study Duration**	**Doses Tested (mg/kg-d)**	**Effects Observed at LOAEL**	**NOAEL (mg/kg-d)**	**LOAEL (mg/kg-d)**
					affecting maternal health, limiting the interpretation of the results; thus, developmental effect levels were not determined.		

Table [SEQ Table * ARABIC]. Summary of Noncancer Data for Oral Exposure to PFBS (CASRN 375-73-5) and the Related Compound K^+PFBS (CASRN 29420-49-3)

Exposure Duration[a]	Reference	Study Confidence	Number of Male/Female, Strain, Species, Study Type, Study Duration	Doses Tested (mg/kg-d)	Effects Observed at LOAEL	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)
Reproductive	[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578545"]; [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=4289686"]; [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=4289697"]; [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=4289740"]	[HYPERLINK "https://hawcprd.epa.gov/rob/study/100001402/"]	30/30, S-D rat, K^+PFBS administered by gavage, two-generation reproductive study	P_0 adults: 0, 30, 100, 300, 1,000 F_1 adults: 0, 30, 100, 300, 1,000	P_0 and F_1 adults: increased incidence of hyperplasia and focal papillary edema in the kidneys of males and females. F_2 pups: no dose-related effects at the highest dose tested (1,000 mg/kg-d).	P_0, F_1: 100 F_2: 1,000	P_0, F_1: 300 F_2: NDr

Table [SEQ Table * ARABIC]. Summary of Noncancer Data for Oral Exposure to PFBS (CASRN 375-73-5) and the Related Compound K^+PFBS (CASRN 29420-49-3)

Exposure Duration[a]	Reference	Study Confidence	Number of Male/Female, Strain, Species, Study Type, Study Duration	Doses Tested (mg/kg-d)	Effects Observed at LOAEL	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)

[a]Duration categories are defined as follows: Acute = exposure for ≤24 hours; short term = repeated exposure for 24 hours to ≤30 days; long term (subchronic) = repeated exposure for >30 days ≤10% lifespan for humans (>30 days up to approximately 90 days in typically used laboratory animal species); chronic = repeated exposure for >10% lifespan for humans (>~90 days to 2 years in typically used laboratory animal species) [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2002</Year><RecNum>1316</RecNum><IDText>88824</IDText><DisplayText>(U.S. EPA, 2002)</DisplayText><record><rec-number>1316</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1316</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>A review of the reference dose and reference concentration processes</title></titles><dates><year>2002</year></dates><pub-location>Washington, DC</pub-location><publisher>U.S. Environmental Protection Agency, Risk Assessment Forum</publisher><isbn>EPA/630/P-02/002F</isbn><label>88824</label><urls><related-urls><url>https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf</url></related-urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>].
[b]Rats were gavaged twice daily at administered doses of 0, 31.3, 62.6, 125, 250, and 500 mg/kg in [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5400978"].

BW = body weight; GD = gestation day; NDr = not determined; ICR = Institute of Cancer Research; K^+PFBS = potassium perfluorobutane sulfonate; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; PFBS = perfluorobutane sulfonic acid; PND = postnatal day; S-D = Sprague-Dawley; T_3 = triiodothyronine; T_4 = thyroxine; TSH = thyroid-stimulating hormone.

5.1 THYROID EFFECTS

PFBS-induced perturbation of the thyroid was consistently observed across two species, sexes, life stages, and exposure durations in two independent, high-confidence studies. These perturbations involved a coherent pattern of hormonal changes. Significant changes in tissue weight or histopathology were not observed.

Similar patterns of decreases in [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-t3-effect-size-animal/"], [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-t4-effect-size-animal/"], and [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-t4-effect-size-animal/"] were observed in PFBS-exposed pregnant mice, nonpregnant adult female and adult male rats from a 28-day study, and gestationally exposed female mouse offspring [ADDIN EN.CITE ADDIN EN.CITE.DATA]. These decreases were statistically significant (~20% in dams and ~50% in offspring) and shown to persist at least 60 days after gestational exposure in offspring and exhibited dose dependence in both studies.

Development of numerous organ systems, including neuronal, reproductive, hepatic, and immune systems, is affected by altered thyroid homeostasis because adequate levels of thyroid hormones are necessary for normal growth and development in early life stages [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Thus, the observed effects of PFBS exposure on thyroid hormone economy are biologically consistent with the reported delays and abnormalities in organ/system development discussed below. It is well established that the presence of sufficient thyroid hormones during the gestational and neonatal period is essential for brain development and maturation. Studies specifically evaluating the effect of PFBS on neurodevelopment were not identified, leaving uncertainty as to the potential for adverse developmental effects. Nonetheless, the coherence of these PFBS findings, in addition to the large number of xenobiotic exposure studies demonstrating associations between thyroid hormone economy and decrements in early life stage growth, development, and survival, provides support for thyroid hazard.

Taken together, the evidence in animals for thyroid effects *supports a hazard*. The single available study in humans did not report an association with thyroid hormones, but had severe limitations hindering its interpretation. This [HYPERLINK "https://hawcprd.epa.gov/rob/study/100515513/"] cross-sectional study was conducted in a highly selected population (i.e., women with premature ovarian insufficiency), had poor sensitivity, and methodological limitations [ADDIN EN.CITE <EndNote><Cite><Author>Zhang</Author><Year>2018</Year><RecNum>447</RecNum><IDText>5079665</IDText><DisplayText>(Zhang et al., 2018)</DisplayText><record><rec-number>447</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604955527">447</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zhang, S.</author><author>Tan, R.</author><author>Pan, R.</author><author>Xiong, J.</author><author>Tian, Y.</author><author>Wu, J.</author><author>Chen, L.</author></authors></contributors><titles><title>Association of perfluoroalkyl and polyfluoroalkyl substances with premature ovarian insufficiency in Chinese women</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-

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EISSN 1945-7197</isbn><accession-num>29986037</accession-num><label>5079665</label><urls><related-urls><url>http://dx.doi.org/10.1210/jc.2017-02783</url></related-urls></urls><electronic-resource-num>10.1210/jc.2017-02783</electronic-resource-num><language>English</language></record></Cite></EndNote>]. The limited evidence for thyroid effects in human studies is *equivocal.* Although there are some differences in hypothalamic-pituitary-thyroid (HPT) regulation across species (e.g., serum hormone-binding proteins, hormone turnover rates, and timing of in utero thyroid development), rodents are generally considered to be a good model for evaluating the potential for thyroid effects of chemicals in humans [ADDIN EN.CITE <EndNote><Cite><Author>Zoeller</Author><Year>2007</Year><RecNum>44</RecNum><IDText>3456414</IDText><DisplayText>(Zoeller et al., 2007)</DisplayText><record><rec-number>44</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604955336">44</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zoeller, R. T.</author><author>Tan, S. W.</author><author>Tyl, R. W.</author></authors></contributors><titles><title>General background on the hypothalamic-pituitary-thyroid (HPT) axis</title><secondary-title>Critical Reviews in Toxicology</secondary-title><alt-title>Crit Rev Toxicol</alt-title><short-title>Critical Reviews in Toxicology</short-title></titles><periodical><full-title>Critical Reviews in Toxicology</full-title><abbr-1>Crit Rev Toxicol</abbr-1></periodical><alt-periodical><full-title>Critical Reviews in Toxicology</full-title><abbr-1>Crit Rev Toxicol</abbr-1></alt-periodical><pages>11-53</pages><volume>37</volume><number>1-2</number><dates><year>2007</year></dates><isbn>ISSN 1040-8444
EISSN 1547-6898</isbn><accession-num>17364704</accession-num><label>3456414</label><work-type>Review</work-type><urls><related-urls><url>http://dx.doi.org/10.1080/10408440601123446</url></related-urls></urls><electronic-resource-num>10.1080/10408440601123446</electronic-resource-num><language>English</language></record></Cite></EndNote>]. For more details pertaining to HPT dynamics and the similarities and differences associated with thyroid hormone economy between rodents and humans, please refer to *A Literature Review of the Current State of the Science Regarding Species Differences in the Control of, and Response to, Thyroid Hormone Perturbations. Part 1: A Human Health Perspective* [ADDIN EN.CITE <EndNote><Cite><Author>Regulatory Science Associates</Author><Year>2019</Year><RecNum>1220</RecNum><DisplayText>(Regulatory Science Associates, 2019)</DisplayText><record><rec-number>1220</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1220</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>Regulatory Science Associates,</author></authors></contributors><titles><title>A literature review of the current

state of the science regarding species differences in the control of, and response to, thyroid hormone perturbations. Part 1: A human health perspective</title></titles><dates><year>2019</year></dates><pub-location>Brussels, Belgium</pub-location><publisher>European Crop Protection Association</publisher><isbn>RSA/ ECPA005_4111_001</isbn><label>6395874</label><urls></urls><language>English</language></record></Cite></EndNote>]. The pattern of decreased thyroid hormones in the absence of a coordinated reflex increase in TSH and commensurate alterations in thyroid tissue weight and/or histology, observed in PFBS studies [e.g., [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"]], is consistent with the human clinical condition referred to as "hypothyroxinemia," which is commonly associated with pregnancy in humans. Hypothyroxinemia has been defined as a low percentile value of FT_4 (ranging from the 2.5th percentile to the 10th percentile of FT_4), with a TSH level within the normal reference range [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Overall, based on findings in animal models considered to be informative for evaluating the potential for thyroid effects in humans, the available evidence *supports a hazard,* and the thyroid is considered a potential target organ for PFBS toxicity in humans.

5.2 DEVELOPMENTAL EFFECTS

Overt effects on birth parameters and early development have generally not been observed in either rats or mice after PFBS exposure. Specifically, the available studies do not provide evidence of effects on endpoints relating to pregnancy loss, fetal survival, or fetal morphology [ADDIN EN.CITE ADDIN EN.CITE.DATA]. While one mouse study indicated pronounced decreases in female offspring BW at several ages after gestational exposure [ADDIN EN.CITE <EndNote><Cite><Author>Feng</Author><Year>2017</Year><RecNum>1031</RecNum><IDText>3856465</IDText><DisplayText>(Feng et al., 2017)</DisplayText><record><rec-number>1031</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1031</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Feng, X.</author><author>Cao, X.</author><author>Zhao, S.</author><author>Wang, X.</author><author>Hua, X.</author><author>Chen, L.</author><author>Chen, L.</author></authors></contributors><titles><title>Exposure of pregnant mice to perfluorobutanesulfonate causes hypothyroxinemia and developmental abnormalities in female offspring</title><secondary-title>Toxicological Sciences</secondary-title><alt-title>Toxicol Sci</alt-title><short-title>Toxicological Sciences</short-title></titles><periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></periodical><alt-periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></alt-periodical><pages>409-419</pages><volume>155</volume><number>2</number><dates><year>2017</year></dates><isbn>ISSN 1096-6080
EISSN 1096-0929</isbn><accession-num>27803384</accession-num><label>3856465</label><urls><related-urls><url>http://dx.doi.org/10.1093/toxsci/kfw219</url></related-urls></urls><electronic-resource-num>10.1093/toxsci/kfw219</electronic-resource-num><language>English</language></record></Cite></EndNote>], several other studies either

did not observe decreases in offspring BW or only detected these changes when parental BWs were similarly affected [ADDIN EN.CITE ADDIN EN.CITE.DATA].

Delays in development have been reported following gestational PFBS exposure in mice, including delayed development of the female reproductive organs (i.e., ovaries, uterus, and vaginal patency), delayed and abnormal estrous cycling (i.e., first estrous and prolongation of diestrus), and delayed eye opening [ADDIN EN.CITE
<EndNote><Cite><Author>Feng</Author><Year>2017</Year><RecNum>1031</RecNum><IDText>3856465</IDText><DisplayText>(Feng et al., 2017)</DisplayText><record><rec-number>1031</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1031</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Feng, X.</author><author>Cao, X.</author><author>Zhao, S.</author><author>Wang, X.</author><author>Hua, X.</author><author>Chen, L.</author><author>Chen, L.</author></authors></contributors><titles><title>Exposure of pregnant mice to perfluorobutanesulfonate causes hypothyroxinemia and developmental abnormalities in female offspring</title><secondary-title>Toxicological Sciences</secondary-title><alt-title>Toxicol Sci</alt-title><short-title>Toxicological Sciences</short-title></titles><periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></periodical><alt-periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></alt-periodical><pages>409-419</pages><volume>155</volume><number>2</number><dates><year>2017</year></dates><isbn>ISSN 1096-6080
EISSN 1096-0929</isbn><accession-num>27803384</accession-num><label>3856465</label><urls><related-urls><url>http://dx.doi.org/10.1093/toxsci/kfw219</url></related-urls></urls><electronic-resource-num>10.1093/toxsci/kfw219</electronic-resource-num><language>English</language></record></Cite></EndNote>
]. Age at vaginal patency and ovarian follicle counts (i.e., in F_1 rat offspring after delivery of the F_2 generation) were unaffected at 1,000 mg/kg-day in a two-generation reproductive toxicity study [ADDIN EN.CITE
<EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1043</RecNum><IDText>1578546</IDText><DisplayText>(Lieder et al., 2009a)</DisplayText><record><rec-number>1043</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1043</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lieder, P. H.</author><author>Chang, S. C.</author><author>York, R. G.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>Toxicological evaluation of potassium perfluorobutanesulfonate in a 90-day oral gavage study with Sprague-Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>45-52</pages><volume>255</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>18992301</accession-num><label>1578546</label><urls><related-

urls><url>http://dx.doi.org/10.1016/j.tox.2008.10.002</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2008.10.002</electronic-resource-num><language>English</language></record></Cite></EndNote>]. This observed lack of effects (i.e., on vaginal patency) is inconsistent with the findings in mice. However, [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"] also noted changes in reproductive hormones that might be relevant to the delays in female sexual development, including a decrease in serum estradiol and increased luteinizing hormone in pubertal offspring (i.e., PND 30 [Note: progesterone was decreased at a later age, PND 60, but not PND 30]). Because the changes reported in mice by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"] were observed in parallel with effects on thyroid hormone levels (discussed above), it is plausible that these developmental delays and hormonal changes could represent sequalae of reduced thyroid function, although that was not directly tested.

For the most part, developmental effects have been reported in a single study and species (mouse); however, the findings are coherent with one another as well as with the consequences of decreased thyroid hormone levels. Because of the coherence across effects on the thyroid and several interrelated developmental effects in mice (i.e., delays and hormonal changes), the evidence in animals for developmental effects *supports a hazard*. There is no reason to expect that the specific developmental delays observed in mice would not be directly relevant to similar processes in humans. Thus, based on findings in animals that are presumed to be relevant to humans, the available evidence *supports a hazard* and the developing offspring is considered a potential target for PFBS toxicity in humans. Because no studies in humans were available that investigated these endpoints, this represents an area deserving of additional research.

5.3 REPRODUCTIVE EFFECTS

Reproductive outcomes, including male and female fertility, pregnancy outcomes, hormone levels, markers of reproductive development, and reproductive organ weights and histopathology, have been evaluated in a number of high-confidence studies in mice [ADDIN EN.CITE <EndNote><Cite><Author>Feng</Author><Year>2017</Year><RecNum>1031</RecNum><IDText>3856465</IDText><DisplayText>(Feng et al., 2017)</DisplayText><record><rec-number>1031</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1031</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Feng, X.</author><author>Cao, X.</author><author>Zhao, S.</author><author>Wang, X.</author><author>Hua, X.</author><author>Chen, L.</author><author>Chen, L.</author></authors></contributors><titles><title>Exposure of pregnant mice to perfluorobutanesulfonate causes hypothyroxinemia and developmental abnormalities in female offspring</title><secondary-title>Toxicological Sciences</secondary-title><alt-title>Toxicol Sci</alt-title><short-title>Toxicological Sciences</short-title></titles><periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></periodical><alt-periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></alt-periodical><pages>409-419</pages><volume>155</volume><number>2</number><dates><year>2017</year></dates><isbn>ISSN 1096-6080
EISSN 1096-0929</isbn><accession-num>27803384</accession-

num><label>3856465</label><urls><related-urls><url>http://dx.doi.org/10.1093/toxsci/kfw219</url></related-urls></urls><electronic-resource-num>10.1093/toxsci/kfw219</electronic-resource-num><language>English</language></record></Cite></EndNote>] and rats [ADDIN EN.CITE ADDIN EN.CITE.DATA]. In addition, five low-confidence human studies evaluated potential associations between PFBS exposure and reproductive effects [ADDIN EN.CITE ADDIN EN.CITE.DATA].

PFBS exposure has resulted in no significant changes in male mating and fertility parameters, reproductive organ weights, or reproductive hormones. Although there were some slight, statistically significant effects on male reproductive endpoints in two rat studies [specifically, altered sperm parameters such as percentage of abnormal sperm or testicular sperm count [ADDIN EN.CITE ADDIN EN.CITE.DATA] and delayed preputial separation at 1,000 mg/kg-day [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1043</RecNum><IDText>1578546</IDText><DisplayText>(Lieder et al., 2009a)</DisplayText><record><rec-number>1043</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1043</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lieder, P. H.</author><author>Chang, S. C.</author><author>York, R. G.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>Toxicological evaluation of potassium perfluorobutanesulfonate in a 90-day oral gavage study with Sprague-Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>45-52</pages><volume>255</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>18992301</accession-num><label>1578546</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2008.10.002</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2008.10.002</electronic-resource-num><language>English</language></record></Cite></EndNote>]], these findings were observed only at the highest doses and the levels of change were of questionable biological significance. No significant reproductive effects in men were noted across two human studies [ADDIN EN.CITE ADDIN EN.CITE.DATA], although U.S. EPA noted a nonsignificant inverse association with testosterone and estradiol in male infants in one study [ADDIN EN.CITE <EndNote><Cite><Author>Yao</Author><Year>2019</Year><RecNum>947</RecNum><DisplayText>(Yao et al., 2019)</DisplayText><record><rec-number>947</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">947</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Yao, Q.</author><author>Shi, R.</author><author>Wang, C.</author><author>Han, W.</author><author>Gao, Y.</author><author>Zhang, Y.</author><author>Zhou, Y.</author><author>Ding, G.</author><author>Tian, Y.</author></authors></contributors><titles><title>Cord blood per-

and polyfluoroalkyl substances, placental steroidogenic enzyme, and cord blood reproductive hormone</title><secondary-title>Environment International</secondary-title><alt-title>Environ Int</alt-title><short-title>Environment International</short-title></titles><periodical><full-title>Environment International</full-title><abbr-1>Environ Int</abbr-1></periodical><alt-periodical><full-title>Environment International</full-title><abbr-1>Environ Int</abbr-1></alt-periodical><pages>573-582</pages><volume>129</volume><number>Elsevier</number><dates><year>2019</year></dates><isbn>ISSN 0160-4120
EISSN 1873-6750</isbn><accession-num>31174145</accession-num><label>5187556</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.envint.2019.03.047</url></related-urls></urls><electronic-resource-num>10.1016/j.envint.2019.03.047</electronic-resource-num><language>English</language></record></Cite></EndNote>].

In general, PFBS exposure in adults has also resulted in no significant alterations in female fertility or pregnancy outcomes in rats or mice [ADDIN EN.CITE ADDIN EN.CITE.DATA] or in two human studies [ADDIN EN.CITE ADDIN EN.CITE.DATA], and inconsistent changes in rodent reproductive organ weights were reported across studies regardless of duration and timing of exposure. However, changes in normal estrous cyclicity, specifically prolongation of the diestrus stage, have been reported in both nonpregnant adult rats exposed to PFBS [ADDIN EN.CITE <EndNote><Cite><Author>NTP</Author><Year>2019</Year><RecNum>1223</RecNum><IDText>5400978</IDText><DisplayText>(NTP, 2019)</DisplayText><record><rec-number>1223</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1223</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NTP,</author></authors></contributors><titles><title>NTP technical report on the toxicity studies of perfluoroalkyl sulfonates (perfluorobutane sulfonic acid, perfluorohexane sulfonate potassium salt, and perfluorooctane sulfonic acid) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats</title></titles><dates><year>2019</year></dates><pub-location>Research Triangle Park, NC</pub-location><isbn>Toxicity Report 96</isbn><label>5400978</label><urls><related-urls><url>https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox096_508.pdf</url></related-urls></urls><language>English</language><modified-date>National Toxicology Program</modified-date></record></Cite></EndNote>] and adult mouse offspring exposed gestationally from GDs 1 to 20 [ADDIN EN.CITE <EndNote><Cite><Author>Feng</Author><Year>2017</Year><RecNum>1031</RecNum><IDText>3856465</IDText><DisplayText>(Feng et al., 2017)</DisplayText><record><rec-number>1031</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1031</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Feng, X.</author><author>Cao, X.</author><author>Zhao, S.</author><author>Wang, X.</author><author>Hua, X.</author><author>Chen, L.</author><author>Chen, L.</author></authors></contributors><titles><title>Exposure of pregnant mice to perfluorobutanesulfonate causes hypothyroxinemia and developmental abnormalities in female offspring</title><secondary-title>Toxicological Sciences</secondary-title><alt-title>Toxicol Sci</alt-title><short-title>Toxicological Sciences</short-title></titles><periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></periodical><alt-

periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></alt-periodical><pages>409-419</pages><volume>155</volume><number>2</number><dates><year>2017</year></dates><isbn>ISSN 1096-6080
EISSN 1096-0929</isbn><accession-num>27803384</accession-num><label>3856465</label><urls><related-urls><url>http://dx.doi.org/10.1093/toxsci/kfw219</url></related-urls></urls><electronic-resource-num>10.1093/toxsci/kfw219</electronic-resource-num><language>English</language></record></Cite></EndNote>]. PFBS exposures in [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5400978"] began between 8 and 10 weeks of age; although the exposures might overlap with some aspects of reproductive development or changes in function during adolescence, these rats were sexually mature and thus the endpoints are considered in the context of reproductive, rather than developmental, effects. The mouse offspring in the study by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"] also displayed delayed vaginal patency and histopathological markers of decreased fertility (i.e., decreased follicles and corpora lutea); however, the reproductive function of those offspring was not tested. While adult rat offspring (F_1) in a two-generation toxicity study also exhibited variable changes in estrous cyclicity [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1044</RecNum><IDText>1578545</IDText><DisplayText>(Lieder et al., 2009b)</DisplayText><record><rec-number>1044</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1044</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lieder, P. H.</author><author>York, R. G.</author><author>Hakes, D. C.</author><author>Chang, S. C.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>A two-generation oral gavage reproduction study with potassium perfluorobutanesulfonate (K+PFBS) in Sprague Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>33-45</pages><volume>259</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>19428941</accession-num><label>1578545</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2009.01.027</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2009.01.027</electronic-resource-num><language>English</language></record></Cite></EndNote>], including prolonged diestrus at 100 mg/kg-day, this effect was not observed at higher doses, limiting interpretation, and no effects on vaginal patency were observed. Female reproductive hormones can inform the potential for effects on reproductive organ development, estrous cyclicity, and fertility. Changes in serum hormones included increased testosterone after exposure of female rats as adults [ADDIN EN.CITE <EndNote><Cite><Author>NTP</Author><Year>2019</Year><RecNum>1223</RecNum><IDText>5400978</IDText><DisplayText>(NTP, 2019)</DisplayText><record><rec-number>1223</rec-number><foreign-keys><key app="EN" db-

id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1223</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NTP,</author></authors></contributors><titles><title>NTP technical report on the toxicity studies of perfluoroalkyl sulfonates (perfluorobutane sulfonic acid, perfluorohexane sulfonate potassium salt, and perfluorooctane sulfonic acid) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats</title></titles><dates><year>2019</year></dates><pub-location>Research Triangle Park, NC</pub-location><isbn>Toxicity Report 96</isbn><label>5400978</label><urls><related-urls><url>https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox096_508.pdf</url></related-urls></urls><language>English</language><modified-date>National Toxicology Program</modified-date></record></Cite></EndNote>], increased luteinizing hormone and decreased estradiol in pubertal mice after gestational exposure [ADDIN EN.CITE <EndNote><Cite><Author>Feng</Author><Year>2017</Year><RecNum>1031</RecNum><IDText>3856465</IDText><DisplayText>(Feng et al., 2017)</DisplayText><record><rec-number>1031</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1031</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Feng, X.</author><author>Cao, X.</author><author>Zhao, S.</author><author>Wang, X.</author><author>Hua, X.</author><author>Chen, L.</author><author>Chen, L.</author></authors></contributors><titles><title>Exposure of pregnant mice to perfluorobutanesulfonate causes hypothyroxinemia and developmental abnormalities in female offspring</title><secondary-title>Toxicological Sciences</secondary-title><alt-title>Toxicol Sci</alt-title><short-title>Toxicological Sciences</short-title></titles><periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></periodical><alt-periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></alt-periodical><pages>409-419</pages><volume>155</volume><number>2</number><dates><year>2017</year></dates><isbn>ISSN 1096-6080
EISSN 1096-0929</isbn><accession-num>27803384</accession-num><label>3856465</label><urls><related-urls><url>http://dx.doi.org/10.1093/toxsci/kfw219</url></related-urls></urls><electronic-resource-num>10.1093/toxsci/kfw219</electronic-resource-num><language>English</language></record></Cite></EndNote>], and decreased estradiol and progesterone when these gestationally exposed mice were assessed as adults. Overall, the pattern and timing of hormonal changes after PFBS exposure is difficult to interpret and likely incomplete. However, the hormonal alterations after gestational PFBS exposure in mice are most relevant to conclusions about female reproductive health.

Taken together, the evidence indicates that the developing reproductive system, particularly in females, might be a target for PFBS toxicity. However, the potential for reproductive effects in adults was less clear, and significant impacts on mating or fertility parameters were not observed across the available studies. Therefore, the evidence in developing animals is considered most informative to conclusions relating to potential developmental effects (see above) and the evidence for reproductive effects (i.e., in adults) is *equivocal.* In the three studies of potential reproductive effects in humans, no clear associations were observed, so the evidence in human studies is *equivocal.* Overall, based on *equivocal* human and animal evidence, the available evidence for reproductive effects is *equivocal.*

5.4 RENAL EFFECTS

Renal effects associated with oral exposure to PFBS have been observed in adult or developing rats across high- or medium-confidence gavage studies of various duration [ADDIN EN.CITE ADDIN EN.CITE.DATA].

Statistically significant increases in kidney weights have been observed in male and female rats after short-term exposure in one study [ADDIN EN.CITE <EndNote><Cite><Author>NTP</Author><Year>2019</Year><RecNum>1223</RecNum><IDText>5400978</IDText><DisplayText>(NTP, 2019)</DisplayText><record><rec-number>1223</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1223</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NTP,</author></authors></contributors><titles><title>NTP technical report on the toxicity studies of perfluoroalkyl sulfonates (perfluorobutane sulfonic acid, perfluorohexane sulfonate potassium salt, and perfluorooctane sulfonic acid) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats</title></titles><dates><year>2019</year></dates><pub-location>Research Triangle Park, NC</pub-location><isbn>Toxicity Report 96</isbn><label>5400978</label><urls><related-urls><url>https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox096_508.pdf</url></related-urls></urls><language>English</language><modified-date>National Toxicology Program</modified-date></record></Cite></EndNote>], with strong dose-dependence for changes in relative weights in female rats at doses as low as 62.6 mg/kg-day. This study was likewise the only study to observe changes in serum markers of renal injury, specifically increased BUN in males at ≥250 mg/kg-day. However, while several other studies noted slight increases in weights, typically at higher PFBS doses (≥500 mg/kg-day), U.S. EPA found that these nonsignificant changes were not consistently observed across the set of available studies and no other studies reported changes in serum markers of renal injury [ADDIN EN.CITE ADDIN EN.CITE.DATA].

Several [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-kidney-effects-kris-v3/"] lesions (i.e., CPN, hydronephrosis, tubular degeneration, and tubular dilation) were unaffected by PFBS exposure in rats, although each of these endpoints was not assessed across several studies [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Mixed results were reported for mineralization and necrosis. Both of these endpoints were noted in females, but not males, after subchronic exposure to 600 mg/kg-day [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1043</RecNum><IDText>1578546</IDText><DisplayText>(Lieder et al., 2009a)</DisplayText><record><rec-number>1043</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1043</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lieder, P. H.</author><author>Chang, S. C.</author><author>York, R. G.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>Toxicological evaluation of potassium perfluorobutanesulfonate in a 90-day oral gavage study with Sprague-Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-

title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>45-52</pages><volume>255</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>18992301</accession-num><label>1578546</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2008.10.002</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2008.10.002</electronic-resource-num><language>English</language></record></Cite></EndNote>], whereas mineralization was unaffected in male or female rats after short-term exposure [ADDIN EN.CITE <EndNote><Cite><Author>3M</Author><Year>2000</Year><RecNum>1257</RecNum><IDText>4289992</IDText><DisplayText>(3M, 2000d)</DisplayText><record><rec-number>1257</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1257</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>3M,</author></authors></contributors><titles><title>A repeated dose range-finding toxicity study of T-7485 in Sprague-Dawley rats</title></titles><dates><year>2000</year></dates><pub-location>St. Paul, MN</pub-location><publisher>3M Pharmaceuticals</publisher><isbn>Study Number: 132-006</isbn><label>4289992</label><urls></urls><language>English</language><modified-date>3M Company</modified-date></record></Cite></EndNote>], and necrosis was unaffected in male or female rats in short-term and two-generation (in both generations) studies [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Multiple markers of inflammatory changes were consistently noted in the two longest exposure duration studies, which were the only studies to report on these endpoints. Specifically, increases in chronic pyelonephritis, tubular basophilia, and mononuclear cell infiltration were observed in female, but not male, rats following subchronic exposure to 600 mg/kg-day [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1043</RecNum><IDText>1578546</IDText><DisplayText>(Lieder et al., 2009a)</DisplayText><record><rec-number>1043</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1043</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lieder, P. H.</author><author>Chang, S. C.</author><author>York, R. G.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>Toxicological evaluation of potassium perfluorobutanesulfonate in a 90-day oral gavage study with Sprague-Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>45-52</pages><volume>255</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>18992301</accession-num><label>1578546</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2008.10.002</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2008.10.002</electronic-resource-

num><language>English</language></record></Cite></EndNote>]. Similarly, increases in papillary edema and hyperplasia were observed in male and female rats after subchronic exposure to 600 mg/kg-day [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1043</RecNum><IDText>1578546</IDText><DisplayText>(Lieder et al., 2009a)</DisplayText><record><rec-number>1043</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1043</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lieder, P. H.</author><author>Chang, S. C.</author><author>York, R. G.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>Toxicological evaluation of potassium perfluorobutanesulfonate in a 90-day oral gavage study with Sprague-Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>45-52</pages><volume>255</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>18992301</accession-num><label>1578546</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2008.10.002</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2008.10.002</electronic-resource-num><language>English</language></record></Cite></EndNote>], and in both generations of rats in the two-generation study at ≥300 mg/kg-day [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1044</RecNum><IDText>1578545</IDText><DisplayText>(Lieder et al., 2009b)</DisplayText><record><rec-number>1044</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1044</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lieder, P. H.</author><author>York, R. G.</author><author>Hakes, D. C.</author><author>Chang, S. C.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>A two-generation oral gavage reproduction study with potassium perfluorobutanesulfonate (K+PFBS) in Sprague Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>33-45</pages><volume>259</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>19428941</accession-num><label>1578545</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2009.01.027</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2009.01.027</electronic-resource-num><language>English</language></record></Cite></EndNote>], with female rats being more sensitive than males.

Overall, the evidence in animals suggests an increased sensitivity of female rats (i.e., based on histopathology and organ-weight changes). Due primarily to the consistency and

coherence in renal effects observed in the subchronic study by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578546"] and the reproductive toxicity study by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578545"] in male and female rats, the evidence in animals *supports a hazard*. There is insufficient evidence in the epidemiology studies of PFBS to inform the human relevance of these findings. Taken together, the renal histopathology evidence in rodents identifies a toxicologically significant spectrum of effects that is presumed to be relevant to similar changes known to occur in humans. Renal effects (i.e., uric acid) were evaluated in one low-confidence human study, and no clear association was observed; therefore, the evidence in human studies is *equivocal*. Overall, based on findings in animals that are presumed to be relevant to humans, the available evidence *supports a hazard* and indicates the kidney as a target organ of PFBS toxicity.

5.5 HEPATIC EFFECTS

Hepatic effects, including organ-weight changes and histopathology associated with oral exposures to PFBS, have been observed in high- or medium-confidence studies in adult or developing rats following short-term- and subchronic-duration exposures [ADDIN EN.CITE ADDIN EN.CITE.DATA] and in a two-generation reproductive study in rats [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1044</RecNum><IDText>1578545</IDText><DisplayText>(Lieder et al., 2009b)</DisplayText><record><rec-number>1044</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1044</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lieder, P. H.</author><author>York, R. G.</author><author>Hakes, D. C.</author><author>Chang, S. C.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>A two-generation oral gavage reproduction study with potassium perfluorobutanesulfonate (K+PFBS) in Sprague Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>33-45</pages><volume>259</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>19428941</accession-num><label>1578545</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2009.01.027</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2009.01.027</electronic-resource-num><language>English</language></record></Cite></EndNote>]. Increased absolute and/or relative liver weights were consistently observed in male and female rats after short-term and multigenerational exposure [ADDIN EN.CITE ADDIN EN.CITE.DATA]. In some studies, the magnitude of the liver-weight changes and the doses at which effects occurred differed across sexes of rat, although the pattern across studies was unclear and did not consistently indicate one sex as more sensitive. Liver histopathology, including necrosis and inflammation, was not consistently observed across PFBS studies. One possible exception is increases in hepatocellular hypertrophy in male rats observed across two studies [ADDIN EN.CITE ADDIN EN.CITE.DATA], although female rats were unaffected in the

multigenerational study and this lesion was not observed at up to 600 mg/kg-day in the subchronic study by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578546"]. The only study to observe changes in serum markers of liver injury was [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5400978"], at ≥250 mg/kg-day in females and ≥500 mg/kg-day in males. The biological relevance or significance of the observed liver effects is not clear. In particular, the adversity of the variable changes in liver weight and observations of cellular hypertrophy is unclear. Further, the observed lesions either occurred in only one sex of rat, were not dose dependent compared with control, and/or occurred only at the highest PFBS dose tested. Thus, the evidence in animals is *equivocal.* Overall, based on *equivocal* animal evidence and a lack of human studies, the available evidence for hepatic effects is *equivocal.*

5.6 EFFECTS ON LIPIDS OR LIPOPROTEINS

Few studies have examined the effects of PFBS on circulating or hepatic lipid or lipoprotein homeostasis. It is recognized that increased circulating levels of lipids and lipoprotein products and/or increased hepatic lipid load are clinical observations of concern in humans. However, the lack of effect on lipid dynamics in most studies of rats exposed to high oral K^+PFBS doses for up to 90 days and the generally modest effects in transgenic mice, fed a high-fat, western-type diet renders this potential health outcome of unclear toxicological significance at this time. Thus, given the inconsistent, modest effects and the unclear biological relevance of these changes in isolation (i.e., lipids/lipoproteins were decreased, not increased) the evidence in animals is *equivocal.* Effects on serum lipids were evaluated in one low-confidence human study and childhood adiposity was evaluated in one medium-confidence study. Although an association was observed between increased PFBS exposure and increased total cholesterol and higher adiposity, this evidence in humans is *equivocal* due to lack of additional supportive evidence. Overall, based on *equivocal* evidence in both animal and human studies, the available evidence for effects on lipid or lipoprotein homeostasis is *equivocal.*

5.7 IMMUNE EFFECTS

Immune effects were observed in two human studies, including associations with asthma [ADDIN EN.CITE <EndNote><Cite><Author>Dong</Author><Year>2013</Year><RecNum>833</RecNum><IDText>1937230</IDText><DisplayText>(Dong et al., 2013a)</DisplayText><record><rec-number>833</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">833</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Dong, G. H.</author><author>Tung, K. Y.</author><author>Tsai, C. H.</author><author>Liu, M. M.</author><author>Wang, D.</author><author>Liu, W.</author><author>Jin, Y. H.</author><author>Hsieh, W. S.</author><author>Lee, Y. L.</author><author>Chen, P. C.</author></authors></contributors><titles><title>Serum polyfluoroalkyl concentrations, asthma outcomes, and immunological markers in a case-control study of Taiwanese children</title><secondary-title>Environmental Health Perspectives</secondary-title><alt-title>Environ Health Perspect</alt-title><short-title>Environmental Health Perspectives</short-title></titles><periodical><full-title>Environmental Health Perspectives</full-title><abbr-1>Environ Health Perspect</abbr-1></periodical><alt-periodical><full-title>Environmental

Health Perspectives</full-title><abbr-1>Environ Health Perspect</abbr-1></alt-periodical><pages>507-13, 513e1-8</pages><volume>121</volume><number>4</number><dates><year>2013</year></dates><isbn>ISSN 0091-6765
EISSN 1552-9924</isbn><accession-num>23309686</accession-num><label>1937230</label><urls><related-urls><url>http://dx.doi.org/10.1289/ehp.1205351</url></related-urls></urls><electronic-resource-num>10.1289/ehp.1205351</electronic-resource-num><language>English</language></record></Cite></EndNote>] and atopic dermatitis [ADDIN EN.CITE <EndNote><Cite><Author>Chen</Author><Year>2018</Year><RecNum>1189</RecNum><IDText>4238372</IDText><DisplayText>(Chen et al., 2018)</DisplayText><record><rec-number>1189</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1189</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Chen, Q.</author><author>Huang, R.</author><author>Hua, L.</author><author>Guo, Y.</author><author>Huang, L.</author><author>Zhao, Y.</author><author>Wang, X.</author><author>Zhang, J.</author></authors></contributors><titles><title>Prenatal exposure to perfluoroalkyl and polyfluoroalkyl substances and childhood atopic dermatitis: A prospective birth cohort study</title><secondary-title>Environmental Health: A Global Access Science Source</secondary-title><alt-title>Environ Health</alt-title><short-title>Environmental Health: A Global Access Science Source</short-title></titles><periodical><full-title>Environmental Health: A Global Access Science Source</full-title><abbr-1>Environ Health</abbr-1></periodical><alt-periodical><full-title>Environmental Health: A Global Access Science Source</full-title><abbr-1>Environ Health</abbr-1></alt-periodical><pages>1-12</pages><volume>17</volume><number>1</number><dates><year>2018</year></dates><isbn>ISSN 1476-069X
EISSN 1476-069X</isbn><accession-num>29343261</accession-num><label>4238372</label><urls><related-urls><url>http://dx.doi.org/10.1186/s12940-018-0352-7</url></related-urls></urls><electronic-resource-num>10.1186/s12940-018-0352-7</electronic-resource-num><language>English</language></record></Cite></EndNote>]. Exposure of human peripheral blood leukocytes or human promyelocytic THP-1 cells to PFBS, in culture, decreased cytokine (e.g., TNFα and IL-10) secretion following antigen challenge [ADDIN EN.CITE <EndNote><Cite><Author>Corsini</Author><Year>2012</Year><RecNum>1047</RecNum><IDText>1937239</IDText><DisplayText>(Corsini et al., 2012)</DisplayText><record><rec-number>1047</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1047</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Corsini, E.</author><author>Sangiovanni, E.</author><author>Avogadro, A.</author><author>Galbiati, V.</author><author>Viviani, B.</author><author>Marinovich, M.</author><author>Galli, C. L.</author><author>Dell'Agli, M.</author><author>Germolec, D. R.</author></authors></contributors><titles><title>In vitro characterization of the immunotoxic potential of several perfluorinated compounds (PFCs)</title><secondary-title>Toxicology and Applied Pharmacology</secondary-title><alt-title>Toxicol Appl Pharmacol</alt-title><short-title>Toxicology and Applied Pharmacology</short-title></titles><periodical><full-title>Toxicology and Applied Pharmacology</full-title><abbr-1>Toxicol Appl Pharmacol</abbr-1></periodical><alt-

periodical><full-title>Toxicology and Applied Pharmacology</full-title><abbr-1>Toxicol Appl Pharmacol</abbr-1></alt-periodical><pages>248-255</pages><volume>258</volume><number>2</number><dates><year>2012</year></dates><isbn>ISSN 0041-008X
EISSN 1096-0333</isbn><accession-num>22119708</accession-num><label>1937239</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.taap.2011.11.004</url></related-urls></urls><electronic-resource-num>10.1016/j.taap.2011.11.004</electronic-resource-num><language>English</language></record></Cite></EndNote>]. Because of the lack of additional evidence and some concerns about potential for residual confounding by other PFAS, the evidence in human studies is *equivocal.* Overall, based on *equivocal* evidence in human studies and a lack of animal studies, the available evidence for immune effects is *equivocal.*

5.8 CARDIOVASCULAR EFFECTS

Cardiovascular effects were observed in two human studies, including associations with cardiovascular disease in adults [ADDIN EN.CITE <EndNote><Cite><Author>Huang</Author><Year>2018</Year><RecNum>290</RecNum><IDText>5024212</IDText><DisplayText>(Huang et al., 2018)</DisplayText><record><rec-number>290</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604955453">290</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Huang, M.</author><author>Jiao, J.</author><author>Zhuang, P.</author><author>Chen, X.</author><author>Wang, J.</author><author>Zhang, Y.</author></authors></contributors><titles><title>Serum polyfluoroalkyl chemicals are associated with risk of cardiovascular diseases in national US population</title><secondary-title>Environment International</secondary-title><alt-title>Environ Int</alt-title><short-title>Environment International</short-title></titles><periodical><full-title>Environment International</full-title><abbr-1>Environ Int</abbr-1></periodical><alt-periodical><full-title>Environment International</full-title><abbr-1>Environ Int</abbr-1></alt-periodical><pages>37-46</pages><volume>119</volume><number>Elsevier</number><dates><year>2018</year></dates><isbn>ISSN 0160-4120
EISSN 1873-6750</isbn><accession-num>29933236</accession-num><label>5024212</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.envint.2018.05.051</url></related-urls></urls><electronic-resource-num>10.1016/j.envint.2018.05.051</electronic-resource-num><language>English</language></record></Cite></EndNote>] and hypertensive disorders in pregnancy [ADDIN EN.CITE <EndNote><Cite><Author>Huang</Author><Year>2019</Year><RecNum>1188</RecNum><IDText>5083564</IDText><DisplayText>(Huang et al., 2019b)</DisplayText><record><rec-number>1188</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1188</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Huang, R.</author><author>Chen, Q.</author><author>Zhang, L.</author><author>Luo, K.</author><author>Chen, L.</author><author>Zhao, S.</author><author>Feng, L.</author><author>Zhang, J.

Source</secondary-title><alt-title>Environ Health</alt-title><short-title>Environmental Health: A Global Access Science Source</short-title></titles><periodical><full-title>Environmental Health: A Global Access Science Source</full-title><abbr-1>Environ Health</abbr-1></periodical><alt-periodical><full-title>Environmental Health: A Global Access Science Source</full-title><abbr-1>Environ Health</abbr-1></alt-periodical><pages>5</pages><volume>18</volume><number>1</number><dates><year>2019</year></dates><isbn>ISSN 1476-069X
EISSN 1476-069X</isbn><accession-num>30626391</accession-num><label>5083564</label><urls><related-urls><url>http://dx.doi.org/10.1186/s12940-018-0445-3</url></related-urls></urls><electronic-resource-num>10.1186/s12940-018-0445-3</electronic-resource-num><language>English</language></record></Cite></EndNote>]. The results are compelling, but as with the evidence for immune effects, there is a lack of additional supportive evidence and some concerns about potential for confounding; thus, the evidence in human studies is *equivocal.* Overall, based on *equivocal* evidence in human studies and a lack of animal studies, the available evidence for cardiovascular effects is *equivocal.*

5.9 EVIDENCE INTEGRATION AND HAZARD CHARACTERIZATION SUMMARY

Based on the evidence integration judgments regarding the potential for PFBS exposure to cause health effects (the narrative above is summarized in [REF _Ref55818151 \h]), the animal studies informing the potential effects of PFBS exposure on thyroid function, renal function, and development were concluded to *support a hazard.* Thus, for the purposes of this assessment, the animal data supporting these outcomes were considered for use in dose-response analysis, and other data were considered no further.

Table [SEQ Table * ARABIC]. Summary of Hazard Characterization and Evidence Integration Judgments				
Studies and Confidence	**Factors That Increase Support for Hazard**	**Factors That Decrease Support for Hazard**	**Summary of Findings**	**Overall Evidence Integration Judgment and Basis**
Thyroid effects				
Human studies				

ED_006316_00006861-00149

• Low-confidence case-control study [ADDIN EN.CITE <EndNote><Cite><Author>Zhang</Author><Year>2018</Year><RecNum>447</RecNum><IDText>5079665</IDText><DisplayText>(Zhang et al., 2018)</DisplayText><record><rec-number>447</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604955527">447</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zhang, S.</author><author>Tan, R.</author><author>Pan, R.</author><author>Xiong, J.</author><author>Tian, Y.</author><author>Wu, J.</author><author>Chen,	• No factors noted.	• Single study of low confidence and poor sensitivity.	No association of PFBS with free T_3, free T_4, or thyroid stimulating hormone, but the study had poor sensitivity and other methodological limitations that hinder interpretability.	*Supports a hazard* (animal evidence *supports a hazard*; human evidence is *equivocal*). The primary basis for this judgment is thyroid hormone decreases in mice and rats at ≥62.6 mg/kg-d.

L.</author></authors></contributors><titles><title>Association of perfluoroalkyl and polyfluoroalkyl substances with premature ovarian insufficiency in Chinese women</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title><alt-title>J Clin Endocrinol Metab</alt-title><short-title>Journal of Clinical Endocrinology and Metabolism</short-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title><abbr-1>J Clin Endocrinol Metab</abbr-1></periodical><alt-periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title><abbr-1>J Clin Endocrinol Metab</abbr-				

Table [SEQ Table * ARABIC]. Summary of Hazard Characterization and Evidence Integration Judgments				
Studies and Confidence	**Factors That Increase Support for Hazard**	**Factors That Decrease Support for Hazard**	**Summary of Findings**	**Overall Evidence Integration Judgment and Basis**
1></alt-periodical><pages>2543-2551</pages><volume>103</volume><number>7</number><dates><year>2018</year></dates><isbn>ISSN 0021-972X
EISSN 1945-7197</isbn><accession-num>29986037</accession-num><label>5079665</label><urls><related-urls><url>http://dx.doi.org/10.1210/jc.2017-02783</url></related-urls></urls><electronic-resource-num>10.1210/jc.2017-02783</electronic-resource-num><language>English</language></record></Cite></EndNote>]				

Table [SEQ Table * ARABIC]. Summary of Hazard Characterization and Evidence Integration Judgments				
Studies and Confidence	**Factors That Increase Support for Hazard**	**Factors That Decrease Support for Hazard**	**Summary of Findings**	**Overall Evidence Integration Judgment and Basis**
[HYPERLINK "https://hawcprd.epa.gov/summary/visual/100000045/"] *(all gavage)*				

Mouse Studies: • High-confidence gestational (GDs 1−20) exposure study [ADDIN EN.CITE <EndNote><Cite><Author>Feng</Author><Year>2017</Year><RecNum>1031</RecNum><IDText>3856465</IDText><DisplayText>(Feng et al., 2017)</DisplayText><record><rec-number>1031</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1031</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Feng, X.</author><author>Cao, X.</author><author>Zhao, S.</author><author>Wang, X.</author><author>Hua, X.</author><author>	• Consistent thyroid hormone decreases (i.e., for total T_3, total T_4, and free T_4) across two high-confidence studies of varied design. The findings were consistent across two species, sexes, life stages, and exposure durations. • Dose-response gradients were observed for those thyroid hormones. • Large magnitudes of effect (e.g., up to ~50% reductions in offspring serum hormones) were reported for those thyroid hormones.	• No factors noted.	Similar patterns of decreases in [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-thyroid-effects/"] (i.e., for [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-t3-effect-size-animal/"], [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-t4-effect-size-animal/"]) were observed in PFBS-exposed pregnant mice and gestationally exposed female mouse offspring at ≥200 mg/kg-d [ADDIN EN.CITE <EndNote><Cite><Author>Feng</Author><Year>2017</Year><RecNum>1031</RecNum><IDText>3856465</IDText><DisplayText>(Feng et al., 2017)</DisplayText><record><rec-number>1031</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1031</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Feng, X.</author><author>Cao, X.</author><author>Zhao, S.</author><author>Wang, X.</author><author>Hua, X.</author><author>Chen, L.</author><author>Chen, L.</author></authors></contributors><titles><title>Exposure of pregnant mice to perfluorobutanesulfonate causes hypothyroxinemia and developmental abnormalities in female offspring</title><secondary-title>Toxicological Sciences</secondary-title><alt-title>Toxicol Sci</alt-title><short-title>Toxicological Sciences</short-title></titles><periodical><full-	

Chen, L.</author><author> Chen, L.</author></authors></contributors><titles><title>Exposure of pregnant mice to perfluorobutanesulfonate causes hypothyroxinemia and developmental abnormalities in female offspring</title><secondary-title>Toxicological Sciences</secondary-title><alt-title>Toxicol Sci</alt-title><short-title>Toxicological Sciences</short-title></titles><periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></periodical><alt-periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></alt-periodical><pages>409-419</pages><volume>155</volume><number>2</number><d			title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></periodical><alt-periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></alt-periodical><pages>409-419</pages><volume>155</volume><number>2</number><dates><year>2017</year></dates><isbn>ISSN 1096-6080
EISSN 1096-0929</isbn><accession-num>27803384</accession-num><label>3856465</label><urls><related-urls><url>http://dx.doi.org/10.1093/toxsci/kfw219</url></related-urls></urls><electronic-resource-num>10.1093/toxsci/kfw219</electronic-resource-num><language>English</language></record></Cite></EndNote>] and in adult female and male rats at ≥62.6 mg/kg-d [ADDIN EN.CITE <EndNote><Cite><Author>NTP</Author><Year>2019</Year><RecNum>1223</RecNum><IDText>5400978</IDText><DisplayText>(NTP, 2019)</DisplayText><record><rec-number>1223</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1223</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NTP,</author></authors></contributors><titles><title>NTP technical report on the toxicity studies of perfluoroalkyl sulfonates (perfluorobutane sulfonic acid, perfluorohexane sulfonate potassium salt, and perfluorooctane sulfonic acid) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats</title></titles><dates><year>2019</year></dates><pub-location>Research Triangle Park, NC</pub-location><isbn>Toxicity Report 96</isbn><label>5400978</label><urls><relat	

ates><year>2017</year></dates><isbn>ISSN 1096-6080
EISSN 1096-0929</isbn><accession-num>27803384</accession-num><label>3856465</label><urls><related-urls><url>http://dx.doi.org/10.1093/toxsci/kfw219</url></related-urls></urls><electronic-resource-num>10.1093/toxsci/kfw219</electronic-resource-num><language>English</language></record></Cite></EndNote>] Rat Studies: • High-confidence short-term (28-d) toxicity study [ADDIN EN.CITE <EndNote><Cite><Author>NTP</Author><Year>2019</Year><RecNum>1223</RecNum><IDText>5400978</IDText><DisplayText>(NTP, 2019)</DisplayText><record><rec-			ed-urls><url>https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox096_508.pdf</url></related-urls></urls><language>English</language><modified-date>National Toxicology Program</modified-date></record></Cite></EndNote>]. Increased [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-tsh-effect-size-animal/"] was reported in mouse dams and in pubertal (PND 30) offspring following gestational exposure [ADDIN EN.CITE <EndNote><Cite><Author>Feng</Author><Year>2017</Year><RecNum>1031</RecNum><IDText>3856465</IDText><DisplayText>(Feng et al., 2017)</DisplayText><record><rec-number>1031</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1031</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Feng, X.</author><author>Cao, X.</author><author>Zhao, S.</author><author>Wang, X.</author><author>Hua, X.</author><author>Chen, L.</author><author>Chen, L.</author></authors></contributors><titles><title>Exposure of pregnant mice to perfluorobutanesulfonate causes hypothyroxinemia and developmental abnormalities in female offspring</title><secondary-title>Toxicological Sciences</secondary-title><alt-title>Toxicol Sci</alt-title><short-title>Toxicological Sciences</short-title></titles><periodical><full-	

number>1223</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1223</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NTP,</author></authors></contributors><titles><title>NTP technical report on the toxicity studies of perfluoroalkyl sulfonates (perfluorobutane sulfonic acid, perfluorohexane sulfonate potassium salt, and perfluorooctane sulfonic acid) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats</title></titles><dates><year>2019</year></dates><pub-location>Research Triangle Park, NC</pub-			title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></periodical><alt-periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></alt-periodical><pages>409-419</pages><volume>155</volume><number>2</number><dates><year>2017</year></dates><isbn>ISSN 1096-6080
EISSN 1096-0929</isbn><accession-num>27803384</accession-num><label>3856465</label><urls><related-urls><url>http://dx.doi.org/10.1093/toxsci/kfw219</url></related-urls></urls><electronic-resource-num>10.1093/toxsci/kfw219</electronic-resource-num><language>English</language></record></Cite></EndNote>], but no changes were noted in rats exposed as adults [ADDIN EN.CITE <EndNote><Cite><Author>NTP</Author><Year>2019</Year><RecNum>1223</RecNum><IDText>5400978</IDText><DisplayText>(NTP, 2019)</DisplayText><record><rec-number>1223</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1223</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NTP,</author></authors></contributors><titles><title>NTP technical report on the toxicity studies of perfluoroalkyl sulfonates (perfluorobutane sulfonic acid, perfluorohexane sulfonate potassium salt, and perfluorooctane sulfonic acid) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats</title></titles><dates><year>2019</year></dates><pub-location>Research Triangle Park, NC</pub-location><isbn>Toxicity Report	

location><isbn>Toxicity Report 96</isbn><label>5400978</label><urls><related-urls><url>https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox096_508.pdf</url></related-urls></urls><language>English</language><modified-date>National Toxicology Program</modified-date></record></Cite></EndNote>]			96</isbn><label>5400978</label><urls><related-urls><url>https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox096_508.pdf</url></related-urls></urls><language>English</language><modified-date>National Toxicology Program</modified-date></record></Cite></EndNote>]. [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-thyroid-effects/"] were not changed after short-term exposure in adult male or female rats [ADDIN EN.CITE <EndNote><Cite><Author>NTP</Author><Year>2019</Year><RecNum>1223</RecNum><IDText>5400978</IDText><DisplayText>(NTP, 2019)</DisplayText><record><rec-number>1223</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1223</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NTP,</author></authors></contributors><titles><title>NTP technical report on the toxicity studies of perfluoroalkyl sulfonates (perfluorobutane sulfonic acid, perfluorohexane sulfonate potassium salt, and perfluorooctane sulfonic acid) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats</title></titles><dates><year>2019</year></dates><pub-location>Research Triangle Park, NC</pub-location><isbn>Toxicity Report 96</isbn><label>5400978</label><urls><related-urls><url>https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox096_508.pdf</url></related-urls></urls><language>English</language><modified-date>National Toxicology	

Table [SEQ Table * ARABIC]. Summary of Hazard Characterization and Evidence Integration Judgments				
Studies and Confidence	**Factors That Increase Support for Hazard**	**Factors That Decrease Support for Hazard**	**Summary of Findings**	**Overall Evidence Integration Judgment and Basis**
			Program</modified-date></record></Cite></EndNote>].	

ED_006316_00006861-00159

Table [SEQ Table * ARABIC]. Summary of Hazard Characterization and Evidence Integration Judgments				
Studies and Confidence	**Factors That Increase Support for Hazard**	**Factors That Decrease Support for Hazard**	**Summary of Findings**	**Overall Evidence Integration Judgment and Basis**
Developmental effects				
Human studies				
No studies available to evaluate.	--	--	--	
[HYPERLINK "https://hawcprd.epa.gov/summary/visual/100000046/"] *(all gavage)*				

Mouse Studies: • High-confidence gestational (GDs 1–20) exposure study [ADDIN EN.CITE <EndNote><Cite><Author>Feng</Author><Year>2017</Year><RecNum>1031</RecNum><IDText>3856465</IDText><DisplayText>(Feng et al., 2017)</DisplayText><record><rec-number>1031</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1031</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Feng, X.</author><author>Cao, X.</author><author>Zhao, S.</author><author>Wang, X.</author><author>Hua, X.</author><author>	• Biologically consistent spectrum of developmental effects in female offspring in a high-confidence mouse study at doses not causing maternal toxicity, including pronounced and persistent effects on BW, delays in developmental milestones and sexual maturation, concordant effects on reproductive organs, and altered serum hormones. • Concerning magnitude of effect (e.g., ~25% change in pup weight) and dose-dependence for several parameters. • Coherence of effects with thyroid hormone insufficiency (see above).	• Developmental effects were limited to changes in one study, sex, and species. • A high-confidence rat study reported some inconsistent evidence, including lack of a delay in vaginal patency and lack of clear effects on estrous cyclicity or ovarian morphology, although the latter endpoint was assessed in much older animals. These potential differences across species are not explainable based on toxicokinetics alone.	In the only mouse study [ADDIN EN.CITE <EndNote><Cite><Author>Feng</Author><Year>2017</Year><RecNum>1031</RecNum><IDText>3856465</IDText><DisplayText>(Feng et al., 2017)</DisplayText><record><rec-number>1031</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1031</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Feng, X.</author><author>Cao, X.</author><author>Zhao, S.</author><author>Wang, X.</author><author>Hua, X.</author><author>Chen, L.</author><author>Chen, L.</author></authors></contributors><titles><title>Exposure of pregnant mice to perfluorobutanesulfonate causes hypothyroxinemia and developmental abnormalities in female offspring</title><secondary-title>Toxicological Sciences</secondary-title><alt-title>Toxicol Sci</alt-title><short-title>Toxicological Sciences</short-title></titles><periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></periodical><alt-periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></alt-periodical><pages>409-419</pages><volume>155</volume><number>2</number><dates><year>2017</year></dates><isbn>ISSN 1096-6080
EISSN 1096-0929</isbn><accession-num>27803384</accession-num><label>3856465</label><urls><related-urls><url>http://dx.doi.org/10.1093/toxsci/kfw2	*Supports a hazard* (animal evidence *supports a hazard*; human evidence is *equivocal*). The primary basis for this judgment is a set of persistent developmental delays and alterations in reproductive system maturation in female mice, generally at ≥200 mg/kg-d.

Chen, L.</author><author> Chen, L.</author></authors></contributors><titles><title>Exposure of pregnant mice to perfluorobutanesulfonate causes hypothyroxinemia and developmental abnormalities in female offspring</title><secondary-title>Toxicological Sciences</secondary-title><alt-title>Toxicol Sci</alt-title><short-title>Toxicological Sciences</short-title></titles><periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></periodical><alt-periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></alt-periodical><pages>409-419</pages><volume>155</volume><number>2</number><d			19</url></related-urls></urls><electronic-resource-num>10.1093/toxsci/kfw219</electronic-resource-num><language>English</language></record></Cite></EndNote>], [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-developmental-effects/"] and altered [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-reproductive-development/"] were observed in female offspring after gestational PFBS exposure, including decreased BW, delayed [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-eye-opening-effect-size-animal/"], delayed [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-vaginal-opening-effect-size-animal/"], altered estrous cyclicity (including prolonged diestrus), [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-reproductive-hormone-effects2/"] (e.g., decreased estradiol and progesterone), and effects on reproductive organs (e.g., weight and [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-female-fertility-effects/"]). Most effects were observed at ≥200 mg/kg-d, with several changes noted at PND 60. Endpoints relating to [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-female-fertility-effects/"] were unchanged in both rats and mice across the four available studies, although this was not tested in mouse offspring	

ates><year>2017</year></dates><isbn>ISSN 1096-6080
EISSN 1096-0929</isbn><accession-num>27803384</accession-num><label>3856465</label><urls><related-urls><url>http://dx.doi.org/10.1093/toxsci/kfw219</url></related-urls></urls><electronic-resource-num>10.1093/toxsci/kfw219</electronic-resource-num><language>English</language></record></Cite></EndNote>] Rat Studies: • Two high-confidence gestational exposure (GDs 6−20) studies: a range-finding study and a follow-up study [ADDIN EN.CITE <EndNote><Cite><Author>York</Author><Year>2002</Year><RecNum>1261</RecNum><IDText>4289675</IDText><			[ADDIN EN.CITE <EndNote><Cite><Author>Feng</Author><Year>2017</Year><RecNum>1031</RecNum><IDText>3856465</IDText><DisplayText>(Feng et al., 2017)</DisplayText><record><rec-number>1031</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1031</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Feng, X.</author><author>Cao, X.</author><author>Zhao, S.</author><author>Wang, X.</author><author>Hua, X.</author><author>Chen, L.</author><author>Chen, L.</author></authors></contributors><titles><title>Exposure of pregnant mice to perfluorobutanesulfonate causes hypothyroxinemia and developmental abnormalities in female offspring</title><secondary-title>Toxicological Sciences</secondary-title><alt-title>Toxicol Sci</alt-title><short-title>Toxicological Sciences</short-title></titles><periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></periodical><alt-periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></alt-periodical><pages>409-419</pages><volume>155</volume><number>2</number><dates><year>2017</year></dates><isbn>ISSN 1096-6080
EISSN 1096-0929</isbn><accession-num>27803384</accession-num><label>3856465</label><urls><related-urls><url>http://dx.doi.org/10.1093/toxsci/kfw2	

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023</isbn><label>4289675</label><urls></urls><language>English</language></record></Cite><Cite><Author>York</Author><Year>2003</Year><RecNum>1260</RecNum><IDText>4289686</IDText><record><rec-number>1260</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1260</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>York, R. G.</author></authors></contributors><titles><title>Oral (gavage) two-generation (one litter per generation) reproduction study of perfluorobutane sulfonate (PFBS) in rats</title></titles><dates><year>2003</year></dates><pub-location>Washington			title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>33-45</pages><volume>259</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>19428941</accession-num><label>1578545</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2009.01.027</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2009.01.027</electronic-resource-num><language>English</language></record></Cite></EndNote>] or observed only at doses causing parental toxicity [ADDIN EN.CITE <EndNote><Cite><Author>York</Author><Year>2002</Year><RecNum>1261</RecNum><IDText>4289675</IDText><DisplayText>(York, 2003c, 2002)</DisplayText><record><rec-number>1261</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1261</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>York, R. G.</author></authors></contributors><titles><title>Oral (gavage) developmental toxicity study of potassium perfluorobutane sulfonate (PFBS) in rats</title></titles><dates><year>2002</year></dates><pub-location>St. Paul, MN</pub-location><publisher>3M Corporate Toxicology</publisher><isbn>Argus Research Protocol Number 418-023</isbn><label>4289675</label><urls></urls><language>English</language></record></Cite><Cite><Author>York</Author><Year>200	

, D.C.</pub-location><publisher>U.S. Environmental Protection Agency</publisher><isbn>Argus Research Protocol Number 418-021</isbn><label>4289686</label><urls></urls><language>English</language></record></Cite></EndNote>] • High-confidence two-generation study [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1044</RecNum><IDText>1578545</IDText><DisplayText>(Lieder et al., 2009b)</DisplayText><record><rec-number>1044</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1044</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors>			3</Year><RecNum>1260</RecNum><IDText>4289686</IDText><record><rec-number>1260</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1260</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>York, R. G.</author></authors></contributors><titles><title>Oral (gavage) two-generation (one litter per generation) reproduction study of perfluorobutane sulfonate (PFBS) in rats</title></titles><dates><year>2003</year></dates><pub-location>Washington, D.C.</pub-location><publisher>U.S. Environmental Protection Agency</publisher><isbn>Argus Research Protocol Number 418-021</isbn><label>4289686</label><urls></urls><language>English</language></record></Cite></EndNote>].	

<authors><author>Lieder, P. H.</author><author>York, R. G.</author><author>Hakes, D. C.</author><author>Chang, S. C.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>A two-generation oral gavage reproduction study with potassium perfluorobutanesulfonate (K+PFBS) in Sprague Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>33-				

Table [SEQ Table * ARABIC]. Summary of Hazard Characterization and Evidence Integration Judgments				
Studies and Confidence	**Factors That Increase Support for Hazard**	**Factors That Decrease Support for Hazard**	**Summary of Findings**	**Overall Evidence Integration Judgment and Basis**
45</pages><volume>259</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>19428941</accession-num><label>1578545</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2009.01.027</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2009.01.027</electronic-resource-num><language>English</language></record></Cite></EndNote>]				

Continued:	Continued: Note: these effects were also coherent with effects on estrous cyclicity observed after short-term exposure in adult rats [ADDIN EN.CITE <EndNote><Cite><Author>NTP</Author><Year>2019</Year><RecNum>1223</RecNum><IDText>5400978</IDText><DisplayText>(NTP, 2019)</DisplayText><record><rec-number>1223</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1223</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NTP,</author></authors></contributors><titles><title>NTP technical report on the toxicity studies of perfluoroalkyl sulfonates (perfluorobutane sulfonic acid, perfluorohexane sulfonate potassium salt, and perfluorooctane sulfonic acid) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats</title></titles><dates><year>2019</year></dates><pub-location>Research Triangle Park, NC</pub-location><isbn>Toxicity Report 96</isbn><label>5400978</lab	Continued:	Continued: In a rat two-generation study, while some statistically significant findings were noted for [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-reproductive-development/"], they were not dose-dependent or were of questionable biological relevance; thus, no clear changes in F_1 offspring were noted at doses up to 1,000 mg/kg-d regarding [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-vaginal-opening-effect-size-animal/"] or estrous cycling at comparable ages to [ADDIN EN.CITE <EndNote><Cite><Author>Feng</Author><Year>2017</Year><RecNum>1031</RecNum><IDText>3856465</IDText><DisplayText>(Feng et al., 2017)</DisplayText><record><rec-number>1031</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1031</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Feng, X.</author><author>Cao, X.</author><author>Zhao, S.</author><author>Wang, X.</author><author>Hua, X.</author><author>Chen, L.</author><author>Chen, L.</author></authors></contributors><titles><title>Exposure of pregnant mice to perfluorobutanesulfonate causes hypothyroxinemia and developmental abnormalities in female offspring</title><secondary-title>Toxicological	Continued:

Table [SEQ Table * ARABIC]. Summary of Hazard Characterization and Evidence Integration Judgments				
Studies and Confidence	**Factors That Increase Support for Hazard**	**Factors That Decrease Support for Hazard**	**Summary of Findings**	**Overall Evidence Integration Judgment and Basis**
	el><urls><related-urls><url>https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox096_508.pdf</url></related-urls></urls><language>English</language><modified-date>National Toxicology Program</modified-date></record></Cite></EndNote>], but this was categorized as a reproductive effect (see below).		Sciences</secondary-title><alt-title>Toxicol Sci</alt-title><short-title>Toxicological Sciences</short-title></titles><periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></periodical><alt-periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></alt-periodical><pages>409-419</pages><volume>155</volume><number>2</number><dates><year>2017</year></dates><isbn>ISSN 1096-6080
EISSN 1096-0929</isbn><accession-num>27803384</accession-num><label>3856465</label><urls><related-urls><url>http://dx.doi.org/10.1093/toxsci/kfw219</url></related-urls></urls><electronic-resource-num>10.1093/toxsci/kfw219</electronic-resource-num><language>English</language></record></Cite></EndNote>], or in ovarian morphology after the F_1 females gave birth to the F_2 pups.	

Table [SEQ Table * ARABIC]. Summary of Hazard Characterization and Evidence Integration Judgments				
Studies and Confidence	**Factors That Increase Support for Hazard**	**Factors That Decrease Support for Hazard**	**Summary of Findings**	**Overall Evidence Integration Judgment and Basis**
Reproductive effects				
[HYPERLINK "https://hawcprd.epa.gov/summary/visual/100000051/"]				
Male reproductive effects				

• Low-confidence cohort study [ADDIN EN.CITE <EndNote><Cite><Author>Zhou</Author><Year>2016</Year><RecNum>956</RecNum><IDText>3856472</IDText><DisplayText>(Zhou et al., 2016)</DisplayText><record><rec-number>956</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">956</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zhou, Y.</author><author>Hu, L. W.</author><author>Qian, Z. M.</author><author>Chang, J. J.</author><author>King, C.</author><author>Paul, G.</author><author>Lin,	• No factors noted.	• Lack of clear association in studies of low confidence with poor sensitivity (i.e., due to low exposure levels, range).	No clear association between PFBS exposure and male reproductive hormones [ADDIN EN.CITE <EndNote><Cite><Author>Zhou</Author><Year>2016</Year><RecNum>956</RecNum><IDText>3856472</IDText><DisplayText>(Zhou et al., 2016)</DisplayText><record><rec-number>956</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">956</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zhou, Y.</author><author>Hu, L. W.</author><author>Qian, Z. M.</author><author>Chang, J. J.</author><author>King, C.</author><author>Paul, G.</author><author>Lin, S.</author><author>Chen, P. C.</author><author>Lee, Y. L.</author><author>Dong, G. H.</author></authors></contributors><titles><title>Association of perfluoroalkyl substances exposure with reproductive hormone levels in adolescents: By sex status</title><secondary-title>Environment International</secondary-title><alt-title>Environ Int</alt-title><short-title>Environment International</short-title></titles><periodical><full-title>Environment International</full-title><abbr-1>Environ Int</abbr-1></periodical><alt-periodical><full-title>Environment International</full-title><abbr-1>Environ Int</abbr-1></alt-periodical><pages>189-195</pages><volume>94</volume><number>Elsevier</number><dates><year>2016</year></dates><isbn>ISSN 0160-4120
EISSN	*Equivocal* (*equivocal* human and animal evidence). Note: As the strongest evidence for female reproductive effects was in offspring that were gestationally exposed, these findings were considered most relevant to developmental, not reproductive, effects.

S.</author><author>Chen, P. C.</author><author>Lee, Y. L.</author><author>Dong, G. H.</author></authors></contributors><titles><title>Association of perfluoroalkyl substances exposure with reproductive hormone levels in adolescents: By sex status</title><secondary-title>Environment International</secondary-title><alt-title>Environ Int</alt-title><short-title>Environment International</short-title></titles><periodical><full-title>Environment International</full-title><abbr-1>Environ Int</abbr-1></periodical><alt-periodical><full-title>Environment International</full-title><abbr-1>Environ Int</abbr-1></alt-periodical><pages>189-195</pages><volume>94</volume><nu			1873-6750</isbn><accession-num>27258660</accession-num><label>3856472</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.envint.2016.05.018</url></related-urls></urls><electronic-resource-num>10.1016/j.envint.2016.05.018</electronic-resource-num><language>English</language></record></Cite></EndNote>] or semen parameters [ADDIN EN.CITE <EndNote><Cite><Author>Song</Author><Year>2018</Year><RecNum>955</RecNum><IDText>4220306</IDText><DisplayText>(Song et al., 2018)</DisplayText><record><rec-number>955</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">955</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Song, X.</author><author>Tang, S.</author><author>Zhu, H.</author><author>Chen, Z.</author><author>Zang, Z.</author><author>Zhang, Y.</author><author>Niu, X.</author><author>Wang, X.</author><author>Yin, H.</author><author>Zeng, F.</author><author>He, C.</author></authors></contributors><titles><title>Biomonitoring PFAAs in blood and semen samples: Investigation of a potential link between PFAAs exposure and semen mobility in China</title><secondary-title>Environment International</secondary-title><alt-title>Environ Int</alt-title><short-title>Environment International</short-	

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EISSN 1873-6750</isbn><accession-num>27258660</accession-num><label>3856472</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.envint.2016.05.018</url></related-urls></urls><electronic-resource-num>10.1016/j.envint.2016.05.018</electronic-resource-num><language>English</language></record></Cite></EndNote>] • Low-confidence cross-sectional study [ADDIN EN.CITE <EndNote><Cite><Author>Song</Author><Year>2018</Year><RecNum>955</RecNum><IDText>4220306</IDText><DisplayText>(Song et al., 2018)</DisplayText><record><rec-number>955</rec-			title></titles><periodical><full-title>Environment International</full-title><abbr-1>Environ Int</abbr-1></periodical><alt-periodical><full-title>Environment International</full-title><abbr-1>Environ Int</abbr-1></alt-periodical><pages>50-54</pages><volume>113</volume><number>Elsevier</number><dates><year>2018</year></dates><isbn>ISSN 0160-4120
EISSN 1873-6750</isbn><accession-num>29421407</accession-num><label>4220306</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.envint.2018.01.010</url></related-urls></urls><electronic-resource-num>10.1016/j.envint.2018.01.010</electronic-resource-num><language>English</language></record></Cite></EndNote>] in adults. A study in newborns reported nonsignificant inverse associations between PFBS exposure and testosterone and estradiol [ADDIN EN.CITE <EndNote><Cite><Author>Yao</Author><Year>2019</Year><RecNum>947</RecNum><DisplayText>(Yao et al., 2019)</DisplayText><record><rec-number>947</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">947</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Yao, Q.</author><author>Shi, R.</author><author>Wang, C.</author><author>Han, W.</author><author>Gao, Y.</author><author>Zhang, Y.</author><author>Zhou,	

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EISSN 1873-6750</isbn><accession-num>29421407</accession-				

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EISSN 1873-6750</isbn><accession-num>31174145</accession-num><label>5187556</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.envint.2019.03.047</url></related-urls></urls><electronic-resource-num>10.1016/j.envint.2019.03.047</electronic-resource-num><language>English</language></record></Cite></EndNote>]				

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Female reproductive effects				

• Low-confidence cross-sectional study [ADDIN EN.CITE <EndNote><Cite><Author>Zhou</Author><Year>2017</Year><RecNum>831</RecNum><DisplayText>(Zhou et al., 2017a)</DisplayText><record><rec-number>831</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">831</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zhou, W.</author><author>Zhang, L.</author><author>Tong, C.</author><author>Fang, F.</author><author>Zhao, S.</author><author>Tian, Y.</author><author>Tao, Y.</author><author>Zhang,	• No factors noted.	• Lack of clear association in studies of low confidence with poor sensitivity (i.e., due to low exposure levels, range). • Potential for reverse causation for menstrual cycle characteristics and premature ovarian insufficiency.	No clear association between PFBS exposure and female reproductive hormones [ADDIN EN.CITE <EndNote><Cite><Author>Zhou</Author><Year>2016</Year><RecNum>956</RecNum><IDText>3856472</IDText><DisplayText>(Zhou et al., 2016)</DisplayText><record><rec-number>956</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">956</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zhou, Y.</author><author>Hu, L. W.</author><author>Qian, Z. M.</author><author>Chang, J. J.</author><author>King, C.</author><author>Paul, G.</author><author>Lin, S.</author><author>Chen, P. C.</author><author>Lee, Y. L.</author><author>Dong, G. H.</author></authors></contributors><titles><title>Association of perfluoroalkyl substances exposure with reproductive hormone levels in adolescents: By sex status</title><secondary-title>Environment International</secondary-title><alt-title>Environ Int</alt-title><short-title>Environment International</short-title></titles><periodical><full-title>Environment International</full-title><abbr-1>Environ Int</abbr-1></periodical><alt-periodical><full-title>Environment International</full-title><abbr-1>Environ Int</abbr-1></alt-periodical><pages>189-195</pages><volume>94</volume><number>Elsevier</number><dates><year>2016</year></dates><isbn>ISSN 0160-4120
EISSN	

J.</author></authors></contributors><titles><title>Plasma perfluoroalkyl and polyfluoroalkyl substances concentration and menstrual cycle characteristics in preconception women</title><secondary-title>Environmental Health Perspectives</secondary-title><alt-title>Environ Health Perspect</alt-title><short-title>Environmental Health Perspectives</short-title></titles><periodical><full-title>Environmental Health Perspectives</full-title><abbr-1>Environ Health Perspect</abbr-1></periodical><alt-periodical><full-title>Environmental Health Perspectives</full-title><abbr-1>Environ Health Perspect</abbr-1></alt-periodical><pages>0			1873-6750</isbn><accession-num>27258660</accession-num><label>3856472</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.envint.2016.05.018</url></related-urls></urls><electronic-resource-num>10.1016/j.envint.2016.05.018</electronic-resource-num><language>English</language></record></Cite></EndNote>] or menstrual cycle characteristics [ADDIN EN.CITE <EndNote><Cite><Author>Song</Author><Year>2018</Year><RecNum>955</RecNum><IDText>4220306</IDText><DisplayText>(Song et al., 2018)</DisplayText><record><rec-number>955</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">955</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Song, X.</author><author>Tang, S.</author><author>Zhu, H.</author><author>Chen, Z.</author><author>Zang, Z.</author><author>Zhang, Y.</author><author>Niu, X.</author><author>Wang, X.</author><author>Yin, H.</author><author>Zeng, F.</author><author>He, C.</author></authors></contributors><titles><title>Biomonitoring PFAAs in blood and semen samples: Investigation of a potential link between PFAAs exposure and semen mobility in China</title><secondary-title>Environment International</secondary-title><alt-title>Environ Int</alt-title><short-title>Environment International</short-	

67012</pages><volume>125</volume><number>6</number><dates><year>2017</year></dates><isbn>ISSN 0091-6765
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Shi, R.</author><author> Wang, C.</author><author> Han, W.</author><author >Gao, Y.</author><author> Zhang, Y.</author><author> Zhou, Y.</author><author> Ding, G.</author><author> Tian, Y.</author></authors ></contributors><titl es><title>Cord blood per- and polyfluoroalkyl substances, placental steroidogenic enzyme, and cord blood reproductive hormone</title><sec ondary-title>Environment International</secon dary-title><alt-title>Environ Int</alt-title><short-title>Environment International</short-title></titles><period ical><full-title>Environment International</full-title><abbr-1>Environ Int</abbr-1></periodical><alt-				

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Table [SEQ Table * ARABIC]. Summary of Hazard Characterization and Evidence Integration Judgments				
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Studies and Confidence	**Factors That Increase Support for Hazard**	**Factors That Decrease Support for Hazard**	**Summary of Findings**	**Overall Evidence Integration Judgment and Basis**
[HYPERLINK "https://hawcprd.epa.gov/summary/visual/100000049/"] *(all gavage)*				
Male reproductive effects				

Rat Studies: • High-confidence short-term (28-d) toxicity study [ADDIN EN.CITE <EndNote><Cite><Author>NTP</Author><Year>2019</Year><RecNum>1223</RecNum><IDText>5400978</IDText><DisplayText>(NTP, 2019)</DisplayText><record><rec-number>1223</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1223</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NTP,</author></authors></contributors><titles><title>NTP technical report on the toxicity studies of perfluoroalkyl sulfonates (perfluorobutane sulfonic acid, perfluorohexane sulfonate potassium	• No factors noted.	• A few small, statistically significant changes were not dose-dependent or were of questionable biological relevance. • Lack of effects on male mating and fertility, hormones, or reproductive organs in rats.	Statistically significant effects on sperm health [ADDIN EN.CITE ADDIN EN.CITE.DATA] and [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-reproductive-development/"] at 1,000 mg/kg-d [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1044</RecNum><IDText>1578545</IDText><DisplayText>(Lieder et al., 2009b)</DisplayText><record><rec-number>1044</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1044</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lieder, P. H.</author><author>York, R. G.</author><author>Hakes, D. C.</author><author>Chang, S. C.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>A two-generation oral gavage reproduction study with potassium perfluorobutanesulfonate (K+PFBS) in Sprague Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>33-45</pages><volume>259</volume><number>1-2</number><dates><year>2009</year></dates	

salt, and perfluorooctane sulfonic acid) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats</title></titles><dates><year>2019</year></dates><pub-location>Research Triangle Park, NC</pub-location><isbn>Toxicity Report 96</isbn><label>5400978</label><urls><related-urls><url>https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox096_508.pdf</url></related-urls></urls><language>English</language><modified-date>National Toxicology Program</modified-date></record></Cite></EndNote>] • High-confidence two-generation study [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1044</RecNum><IDText			><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>19428941</accession-num><label>1578545</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2009.01.027</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2009.01.027</electronic-resource-num><language>English</language></record></Cite></EndNote>] were not observed at lower doses, were within the normal range of historical controls for the laboratory, and/or were no longer significantly changed after correcting for other variables (e.g., BW). Other relevant parameters (e.g., [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-reproductive-organ-effects/"], mating success, and so forth) were unchanged in the three studies.	

>1578545</IDText><DisplayText>(Lieder et al., 2009b)</DisplayText><record><rec-number>1044</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1044</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lieder, P. H.</author><author>York, R. G.</author><author>Hakes, D. C.</author><author>Chang, S. C.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>A two-generation oral gavage reproduction study with potassium perfluorobutanesulfonate (K+PFBS) in Sprague Dawley rats</title><secondary-title>Toxicology</se				

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EISSN 1879-3185</isbn><accession-num>19428941</accession-num><label>1578545</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2009.01.027</url></related-urls></urls><electronic-resource-				

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Butenhoff, J. L.</author></authors></contributors><titles><title>Toxicological evaluation of potassium perfluorobutanesulfonate in a 90-day oral gavage study with Sprague-Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>45-52</pages><volume>255</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
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Table [SEQ Table * ARABIC]. Summary of Hazard Characterization and Evidence Integration Judgments				
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Table [SEQ Table * ARABIC]. Summary of Hazard Characterization and Evidence Integration Judgments				
Studies and Confidence	**Factors That Increase Support for Hazard**	**Factors That Decrease Support for Hazard**	**Summary of Findings**	**Overall Evidence Integration Judgment and Basis**
Female reproductive effects				

ED_006316_00006861-00200

Mouse Studies: • High-confidence gestational (GDs 1−20) exposure study [ADDIN EN.CITE <EndNote><Cite><Author>Feng</Author><Year>2017</Year><RecNum>1031</RecNum><IDText>3856465</IDText><DisplayText>(Feng et al., 2017)</DisplayText><record><rec-number>1031</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1031</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Feng, X.</author><author>Cao, X.</author><author>Zhao, S.</author><author>Wang, X.</author><author>Hua, X.</author><author>	• Effects on markers of female reproductive function (i.e., estrous cyclicity) were observed in high-confidence studies in rats and mice. • Changes in reproductive serum hormones were observed in female rats (i.e., increased testosterone) and mice (e.g., decreased estradiol and progesterone). Although the pattern of change is difficult to interpret and likely incomplete, there were no conflicting data.	• Lack of similar effects on reproductive function (i.e., estrous cyclicity) in a second high-confidence rat study. • Lack of effects on female fertility or pregnancy measures, although this was untested in prenatally exposed female mouse offspring. • Lack of organ-weight changes in three rat studies. Note: The lack of effects on ovarian follicles in rats did not decrease the support for hazard provided by findings in mice, as the age at endpoint assessment was not comparable.	See "Developmental effects" (above) for findings from [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"] and [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578545"]. Altered [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-reproductive-development/"] (including prolonged diestrus) and [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-reproductive-hormone-effects2/"] were observed in female rats after short-term exposure, primarily at ≥250 mg/kg-d [ADDIN EN.CITE <EndNote><Cite><Author>NTP</Author><Year>2019</Year><RecNum>1223</RecNum><IDText>5400978</IDText><DisplayText>(NTP, 2019)</DisplayText><record><rec-number>1223</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1223</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NTP,</author></authors></contributors><titles><title>NTP technical report on the toxicity studies of perfluoroalkyl sulfonates (perfluorobutane sulfonic acid, perfluorohexane sulfonate potassium salt, and perfluorooctane sulfonic acid) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats</title></titles><dates><year>2019</year></dates><pub-location>Research Triangle Park, NC</pub-location><isbn>Toxicity Report 96</isbn><label>5400978</label><urls><related-urls><url>https://ntp.niehs.nih.gov/ntp/htdocs/s	

Chen, L.</author><author> Chen, L.</author></authors></contributors><titles><title>Exposure of pregnant mice to perfluorobutanesulfonate causes hypothyroxinemia and developmental abnormalities in female offspring</title><secondary-title>Toxicological Sciences</secondary-title><alt-title>Toxicol Sci</alt-title><short-title>Toxicological Sciences</short-title></titles><periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></periodical><alt-periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></alt-periodical><pages>409-419</pages><volume>155</volume><number>2</number><d			t_rpts/tox096_508.pdf</url></related-urls></urls><language>English</language><modified-date>National Toxicology Program</modified-date></record></Cite></EndNote>]. Female reproductive [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-reproductive-organ-effects/"] were reduced in gestationally exposed mouse offspring [ADDIN EN.CITE <EndNote><Cite><Author>Feng</Author><Year>2017</Year><RecNum>1031</RecNum><IDText>3856465</IDText><DisplayText>(Feng et al., 2017)</DisplayText><record><rec-number>1031</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1031</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Feng, X.</author><author>Cao, X.</author><author>Zhao, S.</author><author>Wang, X.</author><author>Hua, X.</author><author>Chen, L.</author><author>Chen, L.</author></authors></contributors><titles><title>Exposure of pregnant mice to perfluorobutanesulfonate causes hypothyroxinemia and developmental abnormalities in female offspring</title><secondary-title>Toxicological Sciences</secondary-title><alt-title>Toxicol Sci</alt-title><short-title>Toxicological Sciences</short-title></titles><periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></periodical><alt-periodical><full-title>Toxicological	

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Renal effects				
[HYPERLINK "https://hawcprd.epa.gov/rob/study/100001468/"]				

• Low-confidence cross-sectional study [ADDIN EN.CITE <EndNote><Cite><Author>Qin</Author><Year>2016</Year><RecNum>857</RecNum><IDText>3981721</IDText><DisplayText>(Qin et al., 2016)</DisplayText><record><rec-number>857</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">857</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Qin, X. D.</author><author>Qian, Z.</author><author>Vaughn, M. G.</author><author>Huang, J.</author><author>Ward, P.</author><author>Zeng, X. W.</author><author>Zhou, Y.</author><author>	• No factors noted.	• Inconsistency across subpopulations in single study. • Single study of low confidence with concern for potential reverse causality.	Overall, there was no clear association for PFBS and uric acid. No association observed between PFBS and uric acid in the total population. Increase in uric acid with increased exposure in boys but decrease for girls (neither was statistically significant).	*Supports a hazard.* (animal evidence *supports a hazard*; human evidence is *equivocal*). The primary basis for this judgment is kidney histopathology in rats, primarily females, at ≥300 mg/kg-d.

Zhu, Y.</author><author> Yuan, P.</author><author> Li, M.</author><author >Bai, Z.</author><author> Paul, G.</author><author> Hao, Y. T.</author><author> Chen, W.</author><author >Chen, P. C.</author><author> Dong, G. H.</author><author> Lee, Y. L.</author></authors ></contributors><titl es><title>Positive associations of serum perfluoroalkyl substances with uric acid and hyperuricemia in children from Taiwan</title><seco ndary-title>Environmental Pollution</secondary -title><alt-title>Environ Pollut</alt-title><short-title>Environmental Pollution</short-title></titles><period ical><full-				

title>Environmental Pollution</full-title><abbr-1>Environ Pollut</abbr-1></periodical><alt-periodical><full-title>Environmental Pollution</full-title><abbr-1>Environ Pollut</abbr-1></alt-periodical><pages>519-524</pages><volume>212</volume><number>Elsevier</number><dates><year>2016</year></dates><isbn>ISSN 0269-7491
EISSN 1873-6424</isbn><accession-num>26970855</accession-num><label>3981721</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.envpol.2016.02.050</url></related-urls></urls><electronic-resource-num>10.1016/j.envpol.2016.02.050</electronic-resource-num><language>English</language></rec				

Table [SEQ Table * ARABIC]. Summary of Hazard Characterization and Evidence Integration Judgments				
Studies and Confidence	**Factors That Increase Support for Hazard**	**Factors That Decrease Support for Hazard**	**Summary of Findings**	**Overall Evidence Integration Judgment and Basis**
ord></Cite></EndNote>]				
[HYPERLINK "https://hawcprd.epa.gov/summary/visual/100000047/"] *(all gavage)*				

Rat Studies: • One high-confidence subchronic study [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1043</RecNum><IDText>1578546</IDText><DisplayText>(Lieder et al., 2009a)</DisplayText><record><rec-number>1043</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1043</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lieder, P. H.</author><author>Chang, S. C.</author><author>York, R. G.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>Toxicological evaluation of potassium	• Two high-confidence studies with the longest exposure durations reported consistent effects on kidney histopathology in male and female rats (females were more sensitive). • The histopathological effects related to inflammation were largely dose-dependent and of a concerning magnitude, although primarily at high doses (300 or 600 mg/kg-d).	• Inconsistency in kidney-weight changes across studies. • Findings are from a single laboratory and species. Note: The general lack of effects on other pathology endpoints in the shorter term studies was not considered to decrease support for hazard, as this was not interpreted as inconsistent.	Increases in [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-kidney-weight-effect-size-animal/"] in male and female rats were observed in one short-term study at ≥ 62.6 mg/kg-d, but clear changes were not observed in the other short-term, subchronic, or two-generation rat studies. [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-kidney-effects-kris-v3/"] for some effects (i.e., CPN, hydronephrosis, tubular degeneration, and tubular dilation) was unchanged in single-study evaluations, and mixed results across studies were reported for mineralization and necrosis [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Multiple [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-kidney-histopathology-effect-size-animal/"] and most notably papillary edema and hyperplasia were increased in the two longest duration studies [ADDIN EN.CITE ADDIN EN.CITE.DATA], without contrary evidence.	

perfluorobutanesulfonate in a 90-day oral gavage study with Sprague-Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>45-52</pages><volume>255</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>18992301</accession-num><label>1578546</label><urls><rela				

ted-urls><url>http://dx.doi.org/10.1016/j.tox.2008.10.002</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2008.10.002</electronic-resource-num><language>English</language></record></Cite></EndNote>] • Two high-confidence study [ADDIN EN.CITE <EndNote><Cite><Author>NTP</Author><Year>2019</Year><RecNum>1223</RecNum><IDText>5400978</IDText><DisplayText>(NTP, 2019; 3M, 2001)</DisplayText><record><rec-number>1223</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1223</key></foreign-keys><ref-type name="Report">27</ref-				

type><contributors><authors><author>NTP,</author></authors></contributors><titles><title>NTP technical report on the toxicity studies of perfluoroalkyl sulfonates (perfluorobutane sulfonic acid, perfluorohexane sulfonate potassium salt, and perfluorooctane sulfonic acid) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats</title></titles><dates><year>2019</year></dates><pub-location>Research Triangle Park, NC</pub-location><isbn>Toxicity Report 96</isbn><label>5400978</label><urls><related-urls><url>https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox096_508.pdf</url></related-urls></urls><language>English</language><modified-				

date>National Toxicology Program</modified-date></record></Cite><Cite><Author>3M</Author><Year>2001</Year><RecNum>602</RecNum><IDText>4241246</IDText><record><rec-number>602</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604955602">602</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>3M,</author></authors></contributors><titles><title>A 28-day oral (gavage) toxicity study of T-7485 in Sprague-Dawley rats</title></titles><dates><year>2001</year></dates><pub-location>St. Paul, MN</pub-location><publisher>3M Corporate Toxicology</publisher><isbn>Study Number: 132-				

007</isbn><label>4241246</label><urls></urls><language>English</language><modified-date>3M Company</modified-date></record></Cite></EndNote>] and one medium-confidence [ADDIN EN.CITE <EndNote><Cite><Author>3M</Author><Year>2000</Year><RecNum>1257</RecNum><IDText>4289992</IDText><DisplayText>(3M, 2000d)</DisplayText><record><rec-number>1257</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1257</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>3M,</author></authors></contributors><titles><title>A repeated dose range-finding toxicity study of T-				

7485 in Sprague-Dawley rats</title></titles><dates><year>2000</year></dates><pub-location>St. Paul, MN</pub-location><publisher>3M Pharmaceuticals</publisher><isbn>Study Number: 132-006</isbn><label>4289992</label><urls></urls><language>English</language><modified-date>3M Company</modified-date></record></Cite></EndNote>] short-term (10−28 d) study • One high-confidence two-generation study [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1044</RecNum><IDText>1578545</IDText><DisplayText>(Lieder et al., 2009b)</DisplayText><record><rec-number>1044</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe2				

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1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>33-45</pages><volume>259</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>19428941</accession-num><label>1578545</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2009.01.027</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2009.01.027</electronic-resource-num><language>English</language></record></Cite></EndNote>]				
Continued:	Continued:	Continued:	Continued:	Continued:

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Studies and Confidence	**Factors That Increase Support for Hazard**	**Factors That Decrease Support for Hazard**	**Summary of Findings**	**Overall Evidence Integration Judgment and Basis**
			Other [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-kidney-effects-kris-v3/"], including BUN and creatinine, were mostly unaffected across studies [ADDIN EN.CITE ADDIN EN.CITE.DATA], although the NTP study did observe effects on BUN in males at ≥250 mg/kg-d.	
Hepatic effects				
Human studies				*Equivocal* (*equivocal* human and animal evidence).
No studies available to evaluate	–	–	–	
[HYPERLINK "https://hawcprd.epa.gov/summary/visual/100000048/"] *(all gavage)*				

Rat Studies: • One high-confidence subchronic study [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1043</RecNum><IDText>1578546</IDText><DisplayText>(Lieder et al., 2009a)</DisplayText><record><rec-number>1043</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1043</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lieder, P. H.</author><author>Chang, S. C.</author><author>York, R. G.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>Toxicological evaluation of potassium	• Consistent changes in liver weights in rats of both sexes across four studies. Although the pattern (e.g., by sex and dose) and magnitude of changes varied across studies, weights were consistently increased.	• Other than liver-weight changes, there were notable unexplained inconsistencies in the findings across studies. • One high-confidence study was entirely inconsistent.[a]	Absolute or relative [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-liver-weights/"] were increased in all studies except the 90-d exposure component of the study by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578546"], which tested doses up to 600 mg/kg-d. Note: 70 d of exposure in this study did elicit effects. Effects generally occurred at ≥300 mg/kg-d, although one study reported effects at lower doses [ADDIN EN.CITE <EndNote><Cite><Author>NTP</Author><Year>2019</Year><RecNum>1223</RecNum><IDText>5400978</IDText><DisplayText>(NTP, 2019; 3M, 2001)</DisplayText><record><rec-number>1223</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1223</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NTP,</author></authors></contributors><titles><title>NTP technical report on the toxicity studies of perfluoroalkyl sulfonates (perfluorobutane sulfonic acid, perfluorohexane sulfonate potassium salt, and perfluorooctane sulfonic acid) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats</title></titles><dates><year>2019</year></dates><pub-location>Research Triangle Park, NC</pub-location><isbn>Toxicity Report 96</isbn><label>5400978</label><urls><related-urls><url>https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox096_508.pdf</url></related-urls></urls><language>English</language><m	

perfluorobutanesulfonate in a 90-day oral gavage study with Sprague-Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>45-52</pages><volume>255</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>18992301</accession-num><label>1578546</label><urls><rela			odified-date>National Toxicology Program</modified-date></record></Cite><Cite><Author>3M</Author><Year>2001</Year><RecNum>602</RecNum><IDText>4241246</IDText><record><rec-number>602</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604955602">602</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>3M,</author></authors></contributors><titles><title>A 28-day oral (gavage) toxicity study of T-7485 in Sprague-Dawley rats</title></titles><dates><year>2001</year></dates><pub-location>St. Paul, MN</pub-location><publisher>3M Corporate Toxicology</publisher><isbn>Study Number: 132-007</isbn><label>4241246</label><urls></urls><language>English</language><modified-date>3M Company</modified-date></record></Cite></EndNote>], and two others [ADDIN EN.CITE <EndNote><Cite><Author>3M</Author><Year>2001</Year><RecNum>602</RecNum><IDText>4241246</IDText><DisplayText>(3M, 2001, 2000d)</DisplayText><record><rec-number>602</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604955602">602</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>3M,</author></authors></contributors><titles><title>A 28-day oral (gavage) toxicity study of T-7485 in Sprague-Dawley rats</title></titles><dates><year>2001</year></dates><pub-location>St. Paul, MN</pub-location><publisher>3M Corporate	

ted-urls><url>http://dx.doi.org/10.1016/j.tox.2008.10.002</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2008.10.002</electronic-resource-num><language>English</language></record></Cite></EndNote>] • Two high-confidence studies [ADDIN EN.CITE <EndNote><Cite><Author>NTP</Author><Year>2019</Year><RecNum>1223</RecNum><IDText>5400978</IDText><DisplayText>(NTP, 2019; 3M, 2001)</DisplayText><record><rec-number>1223</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1223</key></foreign-keys><ref-type name="Report">27</ref-			Toxicology</publisher><isbn>Study Number: 132-007</isbn><label>4241246</label><urls></urls><language>English</language><modified-date>3M Company</modified-date></record></Cite><Cite><Author>3M</Author><Year>2000</Year><RecNum>1257</RecNum><IDText>4289992</IDText><record><rec-number>1257</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1257</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>3M,</author></authors></contributors><titles><title>A repeated dose range-finding toxicity study of T-7485 in Sprague-Dawley rats</title></titles><dates><year>2000</year></dates><pub-location>St. Paul, MN</pub-location><publisher>3M Pharmaceuticals</publisher><isbn>Study Number: 132-006</isbn><label>4289992</label><urls></urls><language>English</language><modified-date>3M Company</modified-date></record></Cite></EndNote>] observed changes at ≥900 mg/kg-d. [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-liver-effects/"] were unchanged in three studies [ADDIN EN.CITE ADDIN EN.CITE.DATA] and increased in one short-term study at ≥250 mg/kg-d [ADDIN EN.CITE <EndNote><Cite><Author>NTP</Author><Year>2019</Year><RecNum>1223</RecNum><IDText>5400978</IDText><DisplayText>(NTP, 2019)</DisplayText><record><rec-number>1223</rec-number><foreign-keys><key app="EN" db-	

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Continued:	Continued:	Continued:	Continued:	Continued:

			[HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-liver-effects/"], specifically hepatocellular hypertrophy and cytoplasmic alterations in males and females [ADDIN EN.CITE <EndNote><Cite><Author>NTP</Author><Year>2019</Year><RecNum>1223</RecNum><IDText>5400978</IDText><DisplayText>(NTP, 2019)</DisplayText><record><rec-number>1223</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1223</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NTP,</author></authors></contributors><titles><title>NTP technical report on the toxicity studies of perfluoroalkyl sulfonates (perfluorobutane sulfonic acid, perfluorohexane sulfonate potassium salt, and perfluorooctane sulfonic acid) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats</title></titles><dates><year>2019</year></dates><pub-location>Research Triangle Park, NC</pub-location><isbn>Toxicity Report 96</isbn><label>5400978</label><urls><related-urls><url>https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox096_508.pdf</url></related-urls></urls><language>English</language><modified-date>National Toxicology Program</modified-date></record></Cite></EndNote>] or hypertrophy in females only [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1043</RecNum><IDText>1578546</IDText><DisplayText>(Lieder et al.,	

			2009a)</DisplayText><record><rec-number>1043</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1043</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lieder, P. H.</author><author>Chang, S. C.</author><author>York, R. G.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>Toxicological evaluation of potassium perfluorobutanesulfonate in a 90-day oral gavage study with Sprague-Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>45-52</pages><volume>255</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>18992301</accession-num><label>1578546</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2008.10.002</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2008.10.002</electronic-resource-num><language>English</language></record></Cite></EndNote>], were noted in two studies, but not in the others.	

Table [SEQ Table * ARABIC]. Summary of Hazard Characterization and Evidence Integration Judgments				
Studies and Confidence	**Factors That Increase Support for Hazard**	**Factors That Decrease Support for Hazard**	**Summary of Findings**	**Overall Evidence Integration Judgment and Basis**
Lipid or lipoprotein homeostasis				
[HYPERLINK "https://hawcprd.epa.gov/rob/study/100001071/"]				*Equivocal*

• Low-confidence cross-sectional study [ADDIN EN.CITE <EndNote><Cite><Author>Zeng</Author><Year>2015</Year><RecNum>696</RecNum><IDText>2851005</IDText><DisplayText>(Zeng et al., 2015)</DisplayText><record><rec-number>696</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">696</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zeng, X. W.</author><author>Qian, Z.</author><author>Emo, B.</author><author>Vaughn, M.</author><author>Bao, J.</author><author>Qin, X. D.</author><author>Zhu,	• Statistically significant association in medium-confidence study of adiposity. • Exposure response gradient observed across tertiles for adiposity.	• Single study per outcome. • Potential for residual confounding.	Increase in total cholesterol (statistically significant, β: 19.3 mg/dL increase per unit increase in PFBS) [ADDIN EN.CITE <EndNote><Cite><Author>Zeng</Author><Year>2015</Year><RecNum>696</RecNum><IDText>2851005</IDText><DisplayText>(Zeng et al., 2015)</DisplayText><record><rec-number>696</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">696</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zeng, X. W.</author><author>Qian, Z.</author><author>Emo, B.</author><author>Vaughn, M.</author><author>Bao, J.</author><author>Qin, X. D.</author><author>Zhu, Y.</author><author>Li, J.</author><author>Lee, Y. L.</author><author>Dong, G. H.</author></authors></contributors><titles><title>Association of polyfluoroalkyl chemical exposure with serum lipids in children</title><secondary-title>Science of the Total Environment</secondary-title><alt-title>Sci Total Environ</alt-title><short-title>Science of the Total Environment</short-title></titles><periodical><full-title>Science of the Total Environment</full-title><abbr-1>Sci Total Environ</abbr-1></periodical><alt-periodical><full-title>Science of the Total Environment</full-title><abbr-1>Sci Total Environ</abbr-1></alt-periodical><pages>364-370</pages><volume>512-513</volume><dates><year>2015</year></dates><isbn>ISSN 0048-9697
EISSN 1879-1026</isbn><accession-	(*equivocal* human and animal evidence).

Y.</author><author> Li, J.</author><author> Lee, Y. L.</author><author> Dong, G. H.</author></authors></contributors><titles><title>Association of polyfluoroalkyl chemical exposure with serum lipids in children</title><secondary-title>Science of the Total Environment</secondary-title><alt-title>Sci Total Environ</alt-title><short-title>Science of the Total Environment</short-title></titles><periodical><full-title>Science of the Total Environment</full-title><abbr-1>Sci Total Environ</abbr-1></periodical><alt-periodical><full-title>Science of the Total Environment</full-title><abbr-1>Sci Total Environ</abbr-1></alt-periodical><pages>364-			num>25638651</accession-num><label>2851005</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.scitotenv.2015.01.042</url></related-urls></urls><electronic-resource-num>10.1016/j.scitotenv.2015.01.042</electronic-resource-num><language>English</language></record></Cite></EndNote>]. Higher adiposity in 5-year-old children associated with higher levels of PFBS in cord blood [ADDIN EN.CITE <EndNote><Cite><Author>Chen</Author><Year>2019</Year><RecNum>764</RecNum><IDText>5080578</IDText><DisplayText>(Chen et al., 2019)</DisplayText><record><rec-number>764</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">764</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Chen, Q.</author><author>Zhang, X.</author><author>Zhao, Y.</author><author>Lu, W.</author><author>Wu, J.</author><author>Zhao, S.</author><author>Zhang, J.</author><author>Huang, L.</author></authors></contributors><titles><title>Prenatal exposure to perfluorobutanesulfonic acid and childhood adiposity: A prospective birth cohort study in Shanghai, China</title><secondary-title>Chemosphere</secondary-title><alt-title>Chemosphere</alt-title><short-title>Chemosphere</short-title></titles><periodical><full-title>Chemosphere</full-title><abbr-	

370</pages><volume>512-513</volume><dates><year>2015</year></dates><isbn>ISSN 0048-9697
EISSN 1879-1026</isbn><accession-num>25638651</accession-num><label>2851005</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.scitotenv.2015.01.042</url></related-urls></urls><electronic-resource-num>10.1016/j.scitotenv.2015.01.042</electronic-resource-num><language>English</language></record></Cite></EndNote>] • Medium-confidence study [ADDIN EN.CITE <EndNote><Cite><Author>Chen</Author><Year>2019</Year><RecNum>764</RecNum><IDText>5080578</IDText><DisplayText>(Chen et al., 2019)</DisplayText>			1>Chemosphere</abbr-1></periodical><alt-periodical><full-title>Chemosphere</full-title><abbr-1>Chemosphere</abbr-1></alt-periodical><pages>17-23</pages><volume>226</volume><dates><year>2019</year></dates><isbn>ISSN 0045-6535
EISSN 1879-1298</isbn><accession-num>30908964</accession-num><label>5080578</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.chemosphere.2019.03.095</url></related-urls></urls><electronic-resource-num>10.1016/j.chemosphere.2019.03.095</electronic-resource-num><language>English</language></record></Cite></EndNote>].	

<record><rec-number>764</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">764</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Chen, Q.</author><author>Zhang, X.</author><author>Zhao, Y.</author><author>Lu, W.</author><author>Wu, J.</author><author>Zhao, S.</author><author>Zhang, J.</author><author>Huang, L.				

China</title><secondary-title>Chemosphere</secondary-title><alt-title>Chemosphere</alt-title><short-title>Chemosphere</short-title></titles><periodical><full-title>Chemosphere</full-title><abbr-1>Chemosphere</abbr-1></periodical><alt-periodical><full-title>Chemosphere</full-title><abbr-1>Chemosphere</abbr-1></alt-periodical><pages>17-23</pages><volume>226</volume><dates><year>2019</year></dates><isbn>ISSN 0045-6535
EISSN 1879-1298</isbn><accession-num>30908964</accession-num><label>5080578</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.chemosphere.2019.03.095</url></related-				

Table [SEQ Table * ARABIC]. Summary of Hazard Characterization and Evidence Integration Judgments				
Studies and Confidence	**Factors That Increase Support for Hazard**	**Factors That Decrease Support for Hazard**	**Summary of Findings**	**Overall Evidence Integration Judgment and Basis**
urls></urls><electronic-resource-num>10.1016/j.chemosphere.2019.03.095</electronic-resource-num><language>English</language></record></Cite></EndNote>]				

Table [SEQ Table * ARABIC]. Summary of Hazard Characterization and Evidence Integration Judgments				
Studies and Confidence	**Factors That Increase Support for Hazard**	**Factors That Decrease Support for Hazard**	**Summary of Findings**	**Overall Evidence Integration Judgment and Basis**
[HYPERLINK "https://hawcprd.epa.gov/summary/visual/100000053/"]				

Mouse Studies (diet): • Medium-confidence short-term (4–6 wk) study [ADDIN EN.CITE <EndNote><Cite><Author>Bijland</Author><Year>2011</Year><RecNum>374</RecNum><DisplayText>(Bijland et al., 2011)</DisplayText><record><rec-number>374</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604955493">374</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bijland, S.</author><author>Rensen, P. C. N.</author><author>Pieterman, E. J.</author><author>Maas, A. C. E.</author><author>van der Hoorn, J. W.</author><author>van Erk, M. J.</author><author>Havekes, L.	• Decreases in serum cholesterol and triglycerides were observed in male rats and mice.	• Inconsistent evidence in other rat studies and across sexes. • Small effect magnitudes and unclear direction (decreases) of changes are of questionable biological relevance and could not be informed by evaluating dose-dependency (i.e., only single-dose or high-dose effects were observed).	[HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-lipid-effects/"], specifically cholesterol and triglyceride levels, were slightly decreased (~20%) at 900 mg/kg-d in males, but not females, in one rat study [ADDIN EN.CITE <EndNote><Cite><Author>3M</Author><Year>2001</Year><RecNum>602</RecNum><IDText>4241246</IDText><DisplayText>(3M, 2001)</DisplayText><record><rec-number>602</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604955602">602</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>3M,</author></authors></contributors><titles><title>A 28-day oral (gavage) toxicity study of T-7485 in Sprague-Dawley rats</title></titles><dates><year>2001</year></dates><pub-location>St. Paul, MN</pub-location><publisher>3M Corporate Toxicology</publisher><isbn>Study Number: 132-007</isbn><label>4241246</label><urls></urls><language>English</language><modified-date>3M Company</modified-date></record></Cite></EndNote>], but not in two other rat studies at up to 1,000 mg/kg-d. Serum and hepatic lipids and lipoproteins were also decreased in male mice exposed to ~30 mg/kg-d in diet.	

M.</author><author>Willems van Dijk, K.</author><author>Chang, S. C.</author><author>Ehresman, D. J.</author><author>Butenhoff, J. L.</author><author>Princen, H. M. G.</author></authors></contributors><titles><title>Perfluoroalkyl sulfonates cause alkyl chain length-dependent hepatic steatosis and hypolipidemia mainly by impairing lipoprotein production in APOE*3-Leiden CETP mice</title><secondary-title>Toxicological Sciences</secondary-title><alt-title>Toxicol Sci</alt-title><short-title>Toxicological Sciences</short-title></titles><periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></periodical><alt-periodical><full-				

title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></alt-periodical><pages>290-303</pages><volume>123</volume><number>1</number><dates><year>2011</year></dates><isbn>ISSN 1096-6080
EISSN 1096-0929</isbn><accession-num>21705711</accession-num><label>1578502</label><urls><related-urls><url>http://dx.doi.org/10.1093/toxsci/kfr142</url></related-urls></urls><electronic-resource-num>10.1093/toxsci/kfr142</electronic-resource-num><language>English</language></record></Cite></EndNote>]; transgenic mice (human-like lipid metabolism) were fed a high-fat diet				
Rat Studies (all gavage):				

• One high-confidence subchronic study [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1043</RecNum><IDText>1578546</IDText><DisplayText>(Lieder et al., 2009a)</DisplayText><record><rec-number>1043</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1043</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lieder, P. H.</author><author>Chang, S. C.</author><author>York, R. G.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>Toxicological evaluation of potassium perfluorobutanesulfo				

nate in a 90-day oral gavage study with Sprague-Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>45-52</pages><volume>255</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>18992301</accession-num><label>1578546</label><urls><related-				

urls><url>http://dx.doi.org/10.1016/j.tox.2008.10.002</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2008.10.002</electronic-resource-num><language>English</language></record></Cite></EndNote>] • One high-confidence study [ADDIN EN.CITE <EndNote><Cite><Author>3M</Author><Year>2001</Year><RecNum>602</RecNum><IDText>4241246</IDText><DisplayText>(3M, 2001)</DisplayText><record><rec-number>602</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604955602">602</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>3M,</author></author				

s></contributors><titles><title>A 28-day oral (gavage) toxicity study of T-7485 in Sprague-Dawley rats</title></titles><dates><year>2001</year></dates><pub-location>St. Paul, MN</pub-location><publisher>3M Corporate Toxicology</publisher><isbn>Study Number: 132-007</isbn><label>4241246</label><urls></urls><language>English</language><modified-date>3M Company</modified-date></record></Cite></EndNote>] and one medium-confidence [ADDIN EN.CITE <EndNote><Cite><Author>3M</Author><Year>2000</Year><RecNum>1257</RecNum><IDText>4289992</IDText><DisplayText>(3M, 2000d)</DisplayText><record><rec-number>1257</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe2				

9x4xrdxhw9rvdst2prtt" timestamp="1604957801">1257</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>3M,</author></authors></contributors><titles><title>A repeated dose range-finding toxicity study of T-7485 in Sprague-Dawley rats</title></titles><dates><year>2000</year></dates><pub-location>St. Paul, MN</pub-location><publisher>3M Pharmaceuticals</publisher><isbn>Study Number: 132-006</isbn><label>4289992</label><urls></urls><language>English</language><modified-date>3M Company</modified-date></record></Cite></EndNote>] short-term (10−28 d) study				
Immune effects				
[HYPERLINK "https://hawcprd.epa.gov/summary/visual/100000052/"]				

Table [SEQ Table * ARABIC]. Summary of Hazard Characterization and Evidence Integration Judgments				
Studies and Confidence	**Factors That Increase Support for Hazard**	**Factors That Decrease Support for Hazard**	**Summary of Findings**	**Overall Evidence Integration Judgment and Basis**
Asthma				

ED_006316_00006861-00253

• Medium-confidence case-control study [ADDIN EN.CITE ADDIN EN.CITE.DATA]	• Statistically significant association in a medium-confidence study. Note: Increases in eosinophil markers were not interpreted to increase support for hazard, because they were not statistically significant and other markers important to asthma etiology (e.g., IgE) were unchanged.	• Association was observed in a single study with concern regarding the potential for residual confounding (e.g., with other PFAS chemicals).	Statistically significant increase in odds of asthma diagnosis in the previous year (OR: 1.2−1.9) with increased PFBS exposure. Eosinophil markers (i.e., AEC and ECP) were increased with increased PFBS exposure in asthmatics and nonasthmatics; however, these increases did not reach statistical significance. IgE and T-helper cell-specific cytokines were unchanged [ADDIN EN.CITE <EndNote><Cite><Author>Zhu</Author><Year>2016</Year><RecNum>692</RecNum><IDText>3360105</IDText><DisplayText>(Zhu et al., 2016)</DisplayText><record><rec-number>692</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">692</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zhu, Y.</author><author>Qin, X. D.</author><author>Zeng, X. W.</author><author>Paul, G.</author><author>Morawska, L.</author><author>Su, M. W.</author><author>Tsai, C. H.</author><author>Wang, S. Q.</author><author>Lee, Y. L.</author><author>Dong, G. H.</author></authors></contributors><titles><title>Associations of serum perfluoroalkyl acid levels with T-helper cell-specific cytokines in children: By gender and asthma status</title><secondary-title>Science of the Total Environment</secondary-title><alt-title>Sci Total Environ</alt-title><short-title>Science of the Total Environment</short-title></titles><periodical><full-title>Science of the Total Environment</full-title><abbr-1>Sci Total Environ</abbr-1></periodical><alt-	*Equivocal* (*equivocal* human and animal evidence).

Table [SEQ Table * ARABIC]. Summary of Hazard Characterization and Evidence Integration Judgments				
Studies and Confidence	**Factors That Increase Support for Hazard**	**Factors That Decrease Support for Hazard**	**Summary of Findings**	**Overall Evidence Integration Judgment and Basis**
			periodical><full-title>Science of the Total Environment</full-title><abbr-1>Sci Total Environ</abbr-1></alt-periodical><pages>166-173</pages><volume>559</volume><dates><year>2016</year></dates><isbn>ISSN 0048-9697
EISSN 1879-1026</isbn><accession-num>27060656</accession-num><label>3360105</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.scitotenv.2016.03.187</url></related-urls></urls><electronic-resource-num>10.1016/j.scitotenv.2016.03.187</electronic-resource-num><language>English</language></record></Cite></EndNote>].	

Table [SEQ Table * ARABIC]. Summary of Hazard Characterization and Evidence Integration Judgments				
Studies and Confidence	**Factors That Increase Support for Hazard**	**Factors That Decrease Support for Hazard**	**Summary of Findings**	**Overall Evidence Integration Judgment and Basis**
Atopic dermatitis				

ED_006316_00006861-00256

• Medium-confidence cohort study [ADDIN EN.CITE <EndNote><Cite><Author>Chen</Author><Year>2018</Year><RecNum>1189</RecNum><IDText>4238372</IDText><DisplayText>(Chen et al., 2018)</DisplayText><record><rec-number>1189</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1189</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Chen, Q.</author><author>Huang, R.</author><author>Hua, L.</author><author>Guo, Y.</author><author>Huang, L.</author><author>Zhao, Y.</author><author>Wang,	• No factors noted.	• Slight associations were not statistically significant in a single study with concern regarding the potential for residual confounding (e.g., with other PFAS chemicals).	Statistically nonsignificant increase in odds of atopic dermatitis (OR: 1.2) with increased PFBS exposure.	

X.</author><author> Zhang, J.</author></authors ></contributors><titl es><title>Prenatal exposure to perfluoroalkyl and polyfluoroalkyl substances and childhood atopic dermatitis: A prospective birth cohort study</title><second ary-title>Environmental Health: A Global Access Science Source</secondary-title><alt-title>Environ Health</alt-title><short-title>Environmental Health: A Global Access Science Source</short-title></titles><period ical><full-title>Environmental Health: A Global Access Science Source</full-title><abbr-1>Environ Health</abbr-1></periodical><alt-periodical><full-title>Environmental Health: A Global				

Access Science Source</full-title><abbr-1>Environ Health</abbr-1></alt-periodical><pages>1-12</pages><volume>17</volume><number>1</number><dates><year>2018</year></dates><isbn>ISSN 1476-069X
EISSN 1476-069X</isbn><accession-num>29343261</accession-num><label>4238372</label><urls><related-urls><url>http://dx.doi.org/10.1186/s12940-018-0352-7</url></related-urls></urls><electronic-resource-num>10.1186/s12940-018-0352-7</electronic-resource-num><language>English</language></record></Cite></EndNote>]				
Animal studies				

Table [SEQ Table * ARABIC]. Summary of Hazard Characterization and Evidence Integration Judgments				
Studies and Confidence	**Factors That Increase Support for Hazard**	**Factors That Decrease Support for Hazard**	**Summary of Findings**	**Overall Evidence Integration Judgment and Basis**
No studies available to evaluate.	–	–	–	
Cardiovascular effects				
Human studies				

ED_006316_00006861-00260

• Medium-confidence cross-section study [ADDIN EN.CITE <EndNote><Cite><Author>Huang</Author><Year>2018</Year><RecNum>290</RecNum><IDText>5024212</IDText><DisplayText>(Huang et al., 2018)</DisplayText><record><rec-number>290</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604955453">290</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Huang, M.</author><author>Jiao, J.</author><author>Zhuang, P.</author><author>Chen, X.</author><author>Wang, J.</author><author>Zhang, Y.</author></authors></contributors><titl	• Statistically significant associations in medium-confidence studies.	• Single study per outcome.	Higher odds of cardiovascular disease (total and individual types of disease) with PFBS exposure [ADDIN EN.CITE <EndNote><Cite><Author>Huang</Author><Year>2018</Year><RecNum>290</RecNum><IDText>5024212</IDText><DisplayText>(Huang et al., 2018)</DisplayText><record><rec-number>290</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604955453">290</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Huang, M.</author><author>Jiao, J.</author><author>Zhuang, P.</author><author>Chen, X.</author><author>Wang, J.</author><author>Zhang, Y.</author></authors></contributors><titles><title>Serum polyfluoroalkyl chemicals are associated with risk of cardiovascular diseases in national US population</title><secondary-title>Environment International</secondary-title><alt-title>Environ Int</alt-title><short-title>Environment International</short-title></titles><periodical><full-title>Environment International</full-title><abbr-1>Environ Int</abbr-1></periodical><alt-periodical><full-title>Environment International</full-title><abbr-1>Environ Int</abbr-1></alt-periodical><pages>37-46</pages><volume>119</volume><number>Elsevier</number><dates><year>2018</year></dates><isbn>ISSN 0160-4120
EISSN 1873-6750</isbn><accession-num>29933236</accession-num><label>5024212</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.envint.20	*Equivocal* (*equivocal* human and animal evidence).

es><title>Serum polyfluoroalkyl chemicals are associated with risk of cardiovascular diseases in national US population</title><secondary-title>Environment International</secondary-title><alt-title>Environ Int</alt-title><short-title>Environment International</short-title></titles><periodical><full-title>Environment International</full-title><abbr-1>Environ Int</abbr-1></periodical><alt-periodical><full-title>Environment International</full-title><abbr-1>Environ Int</abbr-1></alt-periodical><pages>37-46</pages><volume>119</volume><number>Elsevier</number><dates><year>2018</year></dates><isbn>ISSN 0160-4120
EISSN 1873-6750</isbn><accessi			18.05.051</url></related-urls></urls><electronic-resource-num>10.1016/j.envint.2018.05.051</electronic-resource-num><language>English</language></record></Cite></EndNote>]. Higher odds of hypertensive disorders in pregnancy with higher PFBS exposure [ADDIN EN.CITE <EndNote><Cite><Author>Huang</Author><Year>2019</Year><RecNum>1188</RecNum><IDText>5083564</IDText><DisplayText>(Huang et al., 2019b)</DisplayText><record><rec-number>1188</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1188</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Huang, R.</author><author>Chen, Q.</author><author>Zhang, L.</author><author>Luo, K.</author><author>Chen, L.</author><author>Zhao, S.</author><author>Feng, L.</author><author>Zhang, J.</author></authors></contributors><titles><title>Prenatal exposure to perfluoroalkyl and polyfluoroalkyl substances and the risk of hypertensive disorders of pregnancy</title><secondary-title>Environmental Health: A Global Access Science Source</secondary-title><alt-title>Environ Health</alt-title><short-title>Environmental Health: A Global Access Science Source</short-title></titles><periodical><full-title>Environmental Health: A Global Access Science Source</full-title><abbr-1>Environ	

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801">1188</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Huang, R.</author><author>Chen, Q.</author><author>Zhang, L.</author><author>Luo, K.</author><author>Chen, L.</author><author>Zhao, S.</author><author>Feng, L.</author><author>Zhang, J.</author></authors></contributors><titles><title>Prenatal exposure to perfluoroalkyl and polyfluoroalkyl substances and the risk of hypertensive disorders of pregnancy</title><secondary-title>Environmental Health: A Global Access Science Source</secondary-title><alt-title>Environ Health</alt-title><short-				

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EISSN 1476-069X</isbn><accession-num>30626391</accession-num><label>5083564</label><urls><related-urls><url>http://dx.d				

Table [SEQ Table * ARABIC]. Summary of Hazard Characterization and Evidence Integration Judgments				
Studies and Confidence	**Factors That Increase Support for Hazard**	**Factors That Decrease Support for Hazard**	**Summary of Findings**	**Overall Evidence Integration Judgment and Basis**
oi.org/10.1186/s12940-018-0445-3</url></related-urls></urls><electronic-resource-num>10.1186/s12940-018-0445-3</electronic-resource-num><language>English</language></record></Cite></EndNote>]				
Animal studies				
No studies available to evaluate.	–	–	–	

[a]The lack of liver effects in the subchronic study was not interpreted to significantly reduce support for hazard because the maximum tolerated dose was 600 mg/kg-d, and other studies reported only liver effects at ≥900 mg/kg-d.

AEC = absolute eosinophil count; BUN = blood urea nitrogen; BW = body weight; CPN = chronic progressive nephropathy; ECP = eosinophilic cationic protein; GD = gestation day; IgE = immunoglobulin E; NTP = National Toxicology Program; OR = odds ratio; PFAS = per- and polyfluoroalkyl substances; PFBS = perfluorobutane sulfonic acid; PND = postnatal day; T_3 = triiodothyronine; T_4 = thyroxine; TSH = thyroid stimulating hormone.

ED_006316_00006861-00266

6.0 DERIVATION OF VALUES

The hazard and dose-response database for PFBS and the potassium salt is primarily associated with the oral route of exposure. There are a limited number of dermal studies (see [REF _Ref288392097 \h]) and no known inhalation studies. There are no known studies evaluating potential cancer effects of PFBS. Therefore, only noncancer reference values are derived in this assessment for the oral route.

6.1 DERIVATION OF ORAL REFERENCE DOSES

The hazards of potential concern for oral PFBS exposure include thyroid, developmental, and kidney effects. Overall, the evidence *supports a hazard* for thyroid, developmental, and kidney effects based on the evidence from animal studies. The limited evidence for thyroid or renal effects in human studies is *equivocal,* and no studies evaluating developmental effects following PFBS exposure in humans were available. Thus, data in humans were not considered further, and the available animal studies that evaluated these effects are considered in the derivation of oral RfDs.

6.1.1 Derivation of the Subchronic Oral Reference Dose

6.1.1.1 Estimation of Points of Departure

Effects in the thyroid were considered when determining potential PODs for deriving a subchronic RfD. Similar patterns of decreases in [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-t3-effect-size-animal/"], [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-t4-effect-size-animal/"], and [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-t4-effect-size-animal/"] were observed in PFBS-exposed pregnant mice, nonpregnant adult female rats, adult male rats, and gestationally exposed female mouse offspring [ADDIN EN.CITE ADDIN EN.CITE.DATA]. These decreases were significant (~20% in dams and ~50% in offspring), were shown to persist at least 60 days after gestational exposure in offspring, and they exhibited a clear dose dependence in both studies. Reflex increases in TSH in response to decreased T_4 or T_3 were not observed in male or female rats following 28 days of exposure [ADDIN EN.CITE <EndNote><Cite><Author>NTP</Author><Year>2019</Year><RecNum>1223</RecNum><IDText>5400978</IDText><DisplayText>(NTP, 2019)</DisplayText><record><rec-number>1223</rec-number><foreign-keys><key app="EN" db-id="fttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1223</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NTP,</author></authors></contributors><titles><title>NTP technical report on the toxicity studies of perfluoroalkyl sulfonates (perfluorobutane sulfonic acid, perfluorohexane sulfonate potassium salt, and perfluorooctane sulfonic acid) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats</title></titles><dates><year>2019</year></dates><pub-location>Research Triangle Park, NC</pub-location><isbn>Toxicity Report 96</isbn><label>5400978</label><urls><related-urls><url>https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox096_508.pdf</url></related-urls></urls><language>English</language><modified-date>National Toxicology Program</modified-date></record></Cite></EndNote>]. Such an increase in TSH was

observed in pregnant mice (measured at GD 20) and their corresponding female offspring, at PND 30 only, with an irregular dose-response or time course [ADDIN EN.CITE <EndNote><Cite><Author>Feng</Author><Year>2017</Year><RecNum>1031</RecNum><IDText>3856465</IDText><DisplayText>(Feng et al., 2017)</DisplayText><record><rec-number>1031</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1031</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Feng, X.</author><author>Cao, X.</author><author>Zhao, S.</author><author>Wang, X.</author><author>Hua, X.</author><author>Chen, L.</author><author>Chen, L.</author></authors></contributors><titles><title>Exposure of pregnant mice to perfluorobutanesulfonate causes hypothyroxinemia and developmental abnormalities in female offspring</title><secondary-title>Toxicological Sciences</secondary-title><alt-title>Toxicol Sci</alt-title><short-title>Toxicological Sciences</short-title></titles><periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></periodical><alt-periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></alt-periodical><pages>409-419</pages><volume>155</volume><number>2</number><dates><year>2017</year></dates><isbn>ISSN 1096-6080
EISSN 1096-0929</isbn><accession-num>27803384</accession-num><label>3856465</label><urls><related-urls><url>http://dx.doi.org/10.1093/toxsci/kfw219</url></related-urls></urls><electronic-resource-num>10.1093/toxsci/kfw219</electronic-resource-num><language>English</language></record></Cite></EndNote>]. This pattern of decreased thyroid hormone without a concomitant increase in TSH is consistent with a human clinical condition referred to as “hypothyroxinemia” [ADDIN EN.CITE <EndNote><Cite><Author>Negro</Author><Year>2011</Year><RecNum>997</RecNum><IDText>6813314</IDText><DisplayText>(Negro et al., 2011)</DisplayText><record><rec-number>997</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">997</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Negro, R.</author><author>Soldin, O. P.</author><author>Obregon, M. J.</author><author>Stagnaro-Green, A.</author></authors></contributors><titles><title>Hypothyroxinemia and pregnancy</title><secondary-title>Endocrine Practice</secondary-title><alt-title>Endocr Pract</alt-title><short-title>Endocrine Practice</short-title></titles><periodical><full-title>Endocrine Practice</full-title><abbr-1>Endocr Pract</abbr-1></periodical><alt-periodical><full-title>Endocrine Practice</full-title><abbr-1>Endocr Pract</abbr-1></alt-periodical><pages>422-429</pages><volume>17</volume><number>3</number><dates><year>2011</year></dates><isbn>ISSN 1530-891X
EISSN 1934-2403</isbn><accession-num>21247845</accession-num><label>6813314</label><work-type>Review</work-type><urls><related-urls><url>http://dx.doi.org/10.4158/EP10309.RA</url></related-urls></urls><electronic-resource-num>10.4158/ep10309.Ra</electronic-resource-num><language>English</language></record></Cite></EndNote>]. Importantly, milder forms of thyroid perturbation are up to 10 times more prevalent in human populations than overt gestational hypothyroidism [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Hypothyroxinemia has been associated with impairments in neurodevelopment and/or cognition later in life [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Because the single available

study in humans had severe limitations hindering the interpretation of the relationship between PFBS exposure and thyroid hormone alterations, at this time the available evidence in humans is not able to inform the potential for thyroid effects in humans. This hypothyroxinemia, rather than overt or subclinical hypothyroidism, is further supported by the lack of effect on thyroid weight or tissue architecture in rats after 28 days of PFBS exposure [ADDIN EN.CITE <EndNote><Cite><Author>NTP</Author><Year>2019</Year><RecNum>1223</RecNum><IDText>5400978</IDText><DisplayText>(NTP, 2019)</DisplayText><record><rec-number>1223</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1223</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NTP,</author></authors></contributors><titles><title>NTP technical report on the toxicity studies of perfluoroalkyl sulfonates (perfluorobutane sulfonic acid, perfluorohexane sulfonate potassium salt, and perfluorooctane sulfonic acid) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats</title></titles><dates><year>2019</year></dates><pub-location>Research Triangle Park, NC</pub-location><isbn>Toxicity Report 96</isbn><label>5400978</label><urls><related-urls><url>https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox096_508.pdf</url></related-urls></urls><language>English</language><modified-date>National Toxicology Program</modified-date></record></Cite></EndNote>].

Developmental effects were considered in determining potential PODs for derivation of a subchronic RfD. Specifically, in [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"], developmental delays or abnormalities in growth (i.e., BW and eye opening), reproductive organs (i.e., ovaries, uterus, and vaginal opening), and reproductive cycling (i.e., first estrous and prolongation of diestrus) were observed in mouse offspring. These effects were observed in mice from litters in which thyroid hormone deficiency occurred at PND 1 and then sustained through pubertal and adult periods (i.e., PNDs 30 and 60, respectively). These interrelated developmental effects in mice (i.e., delays and hormonal changes) are coherent with effects on the thyroid and presumed to be directly relevant to similar processes in humans; however, studies evaluating these outcomes in humans are not available.

Effects in the kidney were considered in determining potential PODs for deriving a subchronic RfD. [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578546"] reported mild to moderate hyperplasia in the kidneys of male and female rats following subchronic-duration exposure to PFBS, and [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578545"] found the same effects in the P_0- and F_1-generation animals in their reproductive toxicity study. Other studies evaluating effects in the kidney were of shorter duration and thus less suitable as a candidate principal study. Additional histopathological alterations accompanied the hyperplasia observed in the kidney, including papillary edema and inflammatory changes, specifically increases in chronic pyelonephritis, tubular basophilia, and mononuclear cell infiltration [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Across the reported kidney histopathological effects following PFBS exposure, female rats were generally more sensitive than males.

Selected data sets from studies with multiple exposure levels for thyroid, developmental, and kidney effects were modeled using the U.S. EPA's Benchmark Dose Software (BMDS) Version 2.7. Consistent with the U.S. EPA's *Benchmark Dose Technical Guidance Document* [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2012</Year><RecNum>1309</RecNum><IDText>1239433</IDText><DisplayText>(U.S. EPA, 2012)</DisplayText><record><rec-number>1309</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1309</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Benchmark dose technical guidance</title></titles><dates><year>2012</year></dates><pub-location>Washington, DC</pub-location><publisher>U.S. Environmental Protection Agency, Risk Assessment Forum</publisher><isbn>EPA/100/R-12/001</isbn><label>1239433</label><urls><related-urls><url>https://www.epa.gov/risk/benchmark-dose-technical-guidance</url></related-urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>], the BMD and 95% lower confidence limit on the BMD (BMDL) were estimated using a benchmark response (BMR) to represent a minimal, biologically significant level of change. Based on BMD guidance, in the absence of information regarding the level of change that is considered biologically significant, a BMR of 1 SD from the control mean for continuous data or a BMR of 10% extra risk for dichotomous data is used to estimate the BMD and BMDL, and to facilitate a consistent basis of comparison across endpoints, studies, and assessments. For some types of effects (e.g., frank effects, developmental effects), biological considerations may warrant the use of a BMR of 0.5 SD or lower.

For effects in developing offspring, including thyroid hormone changes, a BMR of 0.5 SD change from the control mean is used for continuous data to account for effects occurring in a sensitive life stage. A 1 SD BMR is also presented as the basis for model comparison as directed in the U.S. EPA *Benchmark Dose Technical Guidance* [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2012</Year><RecNum>1309</RecNum><IDText>1239433</IDText><DisplayText>(U.S. EPA, 2012)</DisplayText><record><rec-number>1309</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1309</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Benchmark dose technical guidance</title></titles><dates><year>2012</year></dates><pub-location>Washington, DC</pub-location><publisher>U.S. Environmental Protection Agency, Risk Assessment Forum</publisher><isbn>EPA/100/R-12/001</isbn><label>1239433</label><urls><related-urls><url>https://www.epa.gov/risk/benchmark-dose-technical-guidance</url></related-urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>].

For thyroid hormone effects in offspring, a biological level of concern was considered in the identification of a BMR. Multiple lines of evidence regarding the degree of thyroid hormone disruption and developmental outcomes in offspring were evaluated. During developmental life stages, such as gestational/fetal and postnatal/early newborn, thyroid hormones are critical in

many physiological processes associated with somatic growth and maturation and with life functions like thermogenesis, pulmonary gas exchange, and cardiac development [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Further, thyroid hormones are critically important in early neurodevelopment because they directly influence neurogenesis, synaptogenesis, and myelination [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Note that evidence from human epidemiological studies examining the association between thyroid hormone economy in pregnant mothers and neurodevelopment in their offspring is inconsistent. Several human epidemiologic studies have demonstrated key relationships between decreased levels of thyroid hormones such as FT_4 in a pregnant woman and in utero and early postnatal life neurodevelopmental status. For example, children born euthyroid but who were exposed to thyroid hormone insufficiency in utero (e.g., ≤10th percentile free T_4), present with cognitive impairments (e.g., decreased intelligence quotient [IQ], increased risk of expressive language) and/or concomitant abnormalities in brain imaging [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Maternal hypothyroxinemia was also associated with adverse motor function and teacher-reported problems of behavior in offspring at 5 years of age [ADDIN EN.CITE <EndNote><Cite><Author>Andersen</Author><Year>2018</Year><RecNum>1109</RecNum><IDText>5035111</IDText><DisplayText>(Andersen et al., 2018)</DisplayText><record><rec-number>1109</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1109</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Andersen, S. L.</author><author>Andersen, S.</author><author>Liew, Z.</author><author>Vestergaard, P.</author><author>Olsen, J.</author></authors></contributors><titles><title>Maternal Thyroid Function in Early Pregnancy and Neuropsychological Performance of the Child at 5 Years of Age</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title><alt-title>J Clin Endocrinol Metab</alt-title><short-title>Journal of Clinical Endocrinology and Metabolism</short-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title><abbr-1>J Clin Endocrinol Metab</abbr-1></periodical><alt-periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title><abbr-1>J Clin Endocrinol Metab</abbr-1></alt-periodical><pages>660-670</pages><volume>103</volume><number>2</number><dates><year>2018</year></dates><isbn>ISSN 0021-972X
EISSN 1945-7197</isbn><accession-num>29220528</accession-num><label>5035111</label><urls><related-urls><url>http://dx.doi.org/10.1210/jc.2017-02171</url></related-urls></urls><electronic-resource-num>10.1210/jc.2017-02171</electronic-resource-num><language>English</language></record></Cite></EndNote>]. Other human epidemiologic studies have not reported significant associations between thyroid hormone status during pregnancy and neurodevelopmental outcomes in offspring. For example, there was no statistically significant association between thyroid status and IQ decrements or neuropsychological parameters in children born to mothers screened and diagnosed with subclinical hypothyroidism [ADDIN EN.CITE ADDIN EN.CITE.DATA] or mothers undergoing treatment for hypothyroxinemia during gestation [ADDIN EN.CITE <EndNote><Cite><Author>Casey</Author><Year>2017</Year><RecNum>990</RecNum><IDText>4138487</IDText><DisplayText>(Casey et al., 2017)</DisplayText><record><rec-number>990</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">990</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Casey, B. M.</author><author>Thom, E. A.</author><author>Peaceman, A. M.</author><author>Varner,

M. W.</author><author>Sorokin, Y.</author><author>Hirtz, D. G.</author><author>Reddy, U. M.</author><author>Wapner, R. J.</author><author>Thorp, J. M.</author><author>Saade, G.</author><author>Tita, A. T.</author><author>Rouse, D. J.</author><author>Sibai, B.</author><author>Iams, J. D.</author><author>Mercer, B. M.</author><author>Tolosa, J.</author><author>Caritis, S. N.</author><author>VanDorsten, J. P.</author></authors></contributors><titles><title>Treatment of subclinical hypothyroidism or hypothyroxinemia in pregnancy</title><secondary-title>New England Journal of Medicine</secondary-title><alt-title>N Engl J Med</alt-title><short-title>New England Journal of Medicine</short-title></titles><periodical><full-title>New England Journal of Medicine</full-title><abbr-1>N Engl J Med</abbr-1></periodical><alt-periodical><full-title>New England Journal of Medicine</full-title><abbr-1>N Engl J Med</abbr-1></alt-periodical><pages>815-825</pages><volume>376</volume><number>9</number><dates><year>2017</year></dates><isbn>ISSN 0028-4793
EISSN 1533-4406</isbn><accession-num>28249134</accession-num><label>4138487</label><urls><related-urls><url>http://dx.doi.org/10.1056/NEJMoa1606205</url></related-urls></urls><electronic-resource-num>10.1056/NEJMoa1606205</electronic-resource-num><language>English</language></record></Cite></EndNote>]. In these studies, the timing of maternal hypothyroxinemia during pregnancy may be a critical consideration for developmental health outcomes in offspring. Studies have observed a relationship between low free T_4 levels in women at 12 weeks gestation, but not 32 weeks gestation, and impaired psychomotor development in their offspring [ADDIN EN.CITE ADDIN EN.CITE.DATA]. In addition, differences in the type of maternal disruption of thyroid homeostasis may affect the interpretation of the human epidemiologic study results. Specifically, aside from overt primary hypothyroidism, there are two primary subcategories of hypothyroidism: (1) subclinical hypothyroidism; and (2) hypothyroxinemia. Subclinical hypothyroidism is characterized by *elevated TSH levels with normal serum T_4 and T_3 concentrations*. In contrast, hypothyroxinemia is characterized by *decreased T_4 with normal serum concentrations of TSH and T_3* [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Maternal T_4 is the primary source of thyroid hormone for a developing human fetus in the first trimester (i.e., little if any maternal T_3 is transferred across the placenta primarily due to high levels of deiodinase 3 activity that catabolizes T_3 to a biologically inactive form). The first trimester is also a critical window for central nervous system development (e.g., neural tube, spinal cord, medulla, pons, thalamus/hypothalamus, etc.). It therefore stands to reason that the health implications may be different for early in utero development if associated with a condition where maternal T_4 (and T_3) concentrations are normal (subclinical hypothyroidism) versus one involving decreased levels of T_4 (hypothyroxinemia).

With regard to what level of decrease in thyroid hormone (e.g., T_4) is sufficient for anatomical and/or functional alterations, particularly in neurodevelopment in fetuses or newborns, several studies have identified a range of T_4 decrements associated with neurodevelopmental health outcomes across humans or experimental rodents. For example, neurodevelopmental and cognitive deficits have been observed in children who experienced a 25% decrease in maternal T_4 during the second trimester in utero [ADDIN EN.CITE <EndNote><Cite><Author>Haddow</Author><Year>1999</Year><RecNum>993</RecNum><IDText>2176</IDText><DisplayText>(Haddow et al., 1999)</DisplayText><record><rec-number>993</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">993</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>Haddow, J. E.</author><author>Palomaki, G. E.</author><author>Allan, W. C.</author><author>Williams, J. R.</author><author>Knight, G. J.</author><author>Gagnon, J.</author><author>O'Heir, C. E.</author><author>Mitchell, M. L.</author><author>Hermos, R. J.</author><author>Waisbren, S. E.</author><author>Faix, J. D.</author><author>Klein, R. Z.</author></authors></contributors><titles><title>Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child</title><secondary-title>New England Journal of Medicine</secondary-title><alt-title>N Engl J Med</alt-title><short-title>New England Journal of Medicine</short-title></titles><periodical><full-title>New England Journal of Medicine</full-title><abbr-1>N Engl J Med</abbr-1></periodical><alt-periodical><full-title>New England Journal of Medicine</full-title><abbr-1>N Engl J Med</abbr-1></alt-periodical><pages>549-555</pages><volume>341</volume><number>8</number><dates><year>1999</year></dates><isbn>ISSN 0028-4793
EISSN 1533-4406</isbn><accession-num>10451459</accession-num><label>2176</label><urls><related-urls><url>http://dx.doi.org/10.1056/NEJM199908193410801</url></related-urls></urls><electronic-resource-num>10.1056/nejm199908193410801</electronic-resource-num><language>English</language></record></Cite></EndNote>]. In other studies, mild to moderate thyroid insufficiency in pregnant women was defined as having serum T_4 levels below the 10th percentile for the study population, which was associated with a 15−30% decrease relative to the corresponding median [ADDIN EN.CITE ADDIN EN.CITE.DATA]. In experimental animals, decreases in mean maternal T_4 levels of ~10−17% during pregnancy and lactation have been found to elicit neurodevelopmental toxicity in rat offspring [ADDIN EN.CITE ADDIN EN.CITE.DATA]. With regard to a general diagnostic criterion to delineate hypothyroxinemia from other types of clinical hypothyroidism, the Controlled Antenatal Thyroid Study (CATS), conducted in a large cohort of pregnant women in Europe, resulted in the identification of a condition referred to as "isolated hypothyroxinemia" and is defined as the presence of free thyroxine (FT_4) below the 2.5th percentile with a thyrotropin (TSH) level within the reference range [ADDIN EN.CITE ADDIN EN.CITE.DATA]. However, there is no clear or consistent biological threshold for T_4 changes specifically associated with untoward developmental health outcomes, so a BMR of 0.5 SD was therefore identified as a default when performing BMD modeling on thyroid hormone alterations in offspring, consistent with U.S. EPA *Benchmark Dose Technical Guidance* [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2012</Year><RecNum>1309</RecNum><IDText>1239433</IDText><DisplayText>(U.S. EPA, 2012)</DisplayText><record><rec-number>1309</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1309</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Benchmark dose technical guidance</title></titles><dates><year>2012</year></dates><pub-location>Washington, DC</pub-location><publisher>U.S. Environmental Protection Agency, Risk Assessment Forum</publisher><isbn>EPA/100/R-12/001</isbn><label>1239433</label><urls><related-urls><url>https://www.epa.gov/risk/benchmark-dose-technical-guidance</url></related-urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>]. Further, while total T_4 (TT_4), free T_4

(FT_4), and TSH dose-response data are BMD modeled (see Table 9), important biological considerations are presented in Section [REF _Ref54958046 \r \h] that delineate TT_4 as the key hormone metric for a developing fetus/neonate.

Significantly decreased thyroid hormone (e.g., T_4 and T_3) was observed in adult rats exposed twice daily to oral K^+PFBS [ADDIN EN.CITE <EndNote><Cite><Author>NTP</Author><Year>2019</Year><RecNum>1223</RecNum><IDText>5400978</IDText><DisplayText>(NTP, 2019)</DisplayText><record><rec-number>1223</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1223</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NTP,</author></authors></contributors><titles><title>NTP technical report on the toxicity studies of perfluoroalkyl sulfonates (perfluorobutane sulfonic acid, perfluorohexane sulfonate potassium salt, and perfluorooctane sulfonic acid) administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats</title></titles><dates><year>2019</year></dates><pub-location>Research Triangle Park, NC</pub-location><isbn>Toxicity Report 96</isbn><label>5400978</label><urls><related-urls><url>https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox096_508.pdf</url></related-urls></urls><language>English</language><modified-date>National Toxicology Program</modified-date></record></Cite></EndNote>] for 28-days, as well as the P_0 (maternal) mice of the [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"] study. No overt signs of traditional hypothyroidism such as increased TSH and increased thyroid tissue weight or histopathology were observed in either adult population. Adult rodents have a considerable reserve thyroid hormone capacity compared with the developing offspring, which depend on their supply from maternal T_4. While there is concern over decreases in thyroid hormone (i.e., hypothyroxinemia) in developmental life stages due to critical endocrine dependency of in utero and neonatal development, the levels at which there is concern for hypothyroxinemia in euthyroid adults is unclear. Therefore, for euthyroid adult rats and mice, a biologically significant level of change was not determined for the BMR because it is unclear what magnitude of hormone perturbation would be considered adverse. Therefore, for thyroid hormone effects in adult rodents, a default BMR of 1 SD from control mean was applied. Section [REF _Ref54958046 \r \h] presents critical distinctions between perturbations in thyroid hormone economy in adults versus developing fetus/neonates, resulting in the use of different BMRs across life stages (e.g., 1 SD for adults, 0.5 SD for newborns).

For kidney hyperplasia data from the subchronic study by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578546"] and the two-generation reproductive toxicity study by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578545"], a BMR of 10% extra risk was used because it is the recommended approach for dichotomous data in the absence of information on the minimally significant level of change.

6.1.1.2 Approach for Animal-Human Extrapolation of Perfluorobutane Sulfonic Acid Dosimetry

As discussed in Section [REF _Ref54958191 \r \h], toxicokinetic data exists for PFBS in relevant animal species (i.e., rats and mice) and humans, such that a data-informed adjustment

approach for estimating the dosimetric adjustment factor (DAF) can be used. In *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2011</Year><RecNum>1311</RecNum><IDText>752972</IDText><DisplayText>(U.S. EPA, 2011b)</DisplayText><record><rec-number>1311</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1311</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Recommended use of body weight 3/4 as the default method in derivation of the oral reference dose</title></titles><pages>1-50</pages><dates><year>2011</year></dates><pub-location>Washington, DC</pub-location><publisher>U.S. Environmental Protection Agency, Risk Assessment Forum, Office of the Science Advisor</publisher><isbn>EPA/100/R-11/0001</isbn><label>752972</label><urls><related-urls><url>https://www.epa.gov/sites/production/files/2013-09/documents/recommended-use-of-bw34.pdf</url></related-urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>], the U.S. EPA endorses a hierarchy of approaches to derive human equivalent oral exposures using data from laboratory animal species, with the preferred approach being physiologically based toxicokinetic modeling. Other approaches might include using chemical-specific information, without a complete physiologically based toxicokinetic model. In the absence of chemical-specific models or data to inform the derivation of human equivalent oral exposures, the U.S. EPA endorses $BW^{3/4}$ as a default to extrapolate toxicologically equivalent doses of orally administered agents from all laboratory animals to humans for the purpose of deriving an RfD under certain exposure conditions.

The U.S. EPA concluded that data for PFBS are adequate to support derivation of data-informed dosimetric adjustment. Briefly, the ratio of the clearance (CL) in humans to animals, CL_H:CL_A, can be used to convert an oral dose-rate in experimental animals (mg/kg-day) to a human equivalent dose rate. Assuming the exposure being evaluated is low enough to be in the linear (or first order) range of clearance, the average blood concentration (C_{AVG}) that results from a given dose is calculated as:

$$C_{AVG}\left({}^{\mathrm{mg}}/_{\mathrm{mL}}\right) = f_{\mathrm{abs}} \times \mathrm{dose}\ (\mathrm{mg/kg/hr}) \Big/ CL\ (\mathrm{mL/kg/hr})$$

where f_{abs} is the fraction absorbed and dose is the average dose rate expressed at an hourly rate. Assuming equal toxicity given equal C_{AVG} in humans as in mice or rats, and that f_{abs} is the same in humans as animals, the equitoxic dose, human equivalent dose (HED) (i.e., the human dose that should yield the same blood concentration (C_{AVG}) as the animal dose from which it is being extrapolated), is then calculated as follows:

$$HED = \frac{POD}{CL_{\mathrm{A}}/CL_{\mathrm{H}}} = POD \times \frac{CL_{\mathrm{H}}}{CL_{\mathrm{A}}}$$

Thus, the DAF could be calculated as simply CL_H:CL_A, the ratio of clearance in humans to clearance in the animal from which the POD is obtained. However, clearance values are not reported for humans in the available toxicokinetic studies for PFBS [ADDIN EN.CITE

ADDIN EN.CITE.DATA]. Because clearance is a measure of average elimination, to calculate clearance in the absence of the information, one also needs to evaluate a companion variable, the V_d. Neither [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"] nor [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6781357"] reported the V_d for humans. However, there is evidence suggesting that V_d for PFBS is relatively similar across species, including rodents (e.g., 0.12−0.29 L/kg across male and female rats following 10 mg/kg i.v. dose) and monkeys (e.g., 0.21−0.25 L/kg across male and female cynomolgus macaques following 10 mg/kg i.v. dose) [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Therefore, it is reasonable to assume V_d for humans is approximately equivalent to V_d for animals (i.e., $V_{d,H} = V_{d,A}$), in which case clearance and half-life are inversely related as follows:

$$CL\ (\mathrm{mL/kg/hr}) = \ln(2) \times \frac{1}{t_{1/2}(\mathrm{hr})} \times V_d\ \left({}^{\mathrm{mL}}/_{\mathrm{kg}}\right)$$

Because reliable measures of half-life in humans and animals are available for PFBS, the ratio of elimination half-life in animals from which the POD is obtained to that in humans, $t_{1/2,A}$:$t_{1/2,H}$, can be used to calculate the DAF, and the human equivalent dose (HED) can be calculated as follows:

$$HED = POD \times \frac{t_{1/2_A}}{t_{1/2_H}}$$

As described in Section [REF _Ref54958221 \r \h], two studies evaluated the elimination of human serum K^+PFBS in human populations with previous occupational exposure [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Initial blood concentrations of PFBS in the population examined by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6781357"] are more representative of environmental exposure, and the population was larger, including 11 male and 6 female employees when compared to [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"]. While the estimated serum half-life of PFBS reported by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"] overlapped with that by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6781357"] (mean: 43.8 days; range: 21.9−87.6 days), there is a statistically significant difference between these two studies. As such, the two data sets will not be combined and the half-life estimated by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6781357"] is presumed to better predict human dosimetry at environmental levels. The average half-life reported by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6781357"] (mean: 43.8 days or 1,050 hours) was assigned for $t_{½,H}$.

One study evaluated the elimination of serum PFBS in mice. [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6579272"] reported

serum terminal half-lives of 5.8 hours in male mice and 4.5 hours in female mice. Because the half-life estimates did not vary significantly between the doses (i.e., 30 and 300 mg/kg), these parameter estimates were combined. However, there was a statistically significant difference in the half-life estimates between sexes (female mice had a slightly shorter half-life [4.5 hours] compared to males [5.8 hours]), so sex-specific half-lives were assigned for $t_{1/2,A}$ for mice.

Two studies were used to calculate serum half-life estimates for dosimetric adjustment in rats [ADDIN EN.CITE ADDIN EN.CITE.DATA]. A numerical average of the terminal half-lives ($t_{1/2,\beta}$) measured in rats after oral and i.v. doses is identified in [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"] as 4.6 hours in males and 5.7 hours in females. [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"] reported sex-specific elimination differences in half-life values in rats. A numerical average of the $t_{1/2,\beta}$ measured in male rats after oral and i.v. doses in [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5387170"] is 4.9 hours. In male rats, half-life values reported in [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"] and [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5387170"] are consistent, thus they were averaged for use in dosimetric adjustment, resulting in a geometric mean terminal serum half-life of 4.8 hours. The terminal half-life value reported by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5387170"] in female rats after a 4-mg/kg i.v. dose of PFBS was 0.95 hours. [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5387170"] was not able to fit the data to a two-compartment model, thus they did not report a $t_{1/2,\beta}$ for rats following oral exposure. For this reason, the mean female $t_{1/2,\beta}$ value from [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"] was used for dosimetric adjustment.

[REF _Ref55818185 \h] presents the DAFs for converting rat and mice PODs to HEDs for PFBS.

Table [SEQ Table * ARABIC]. Mouse, Rat, and Human Half-Lives and Data-Informed DAFs				
Species	**Sex**	**Animal $t_{1/2}$ (hr)**	**Human $t_{1/2}$ (hr)**	**DAF ($t_{1/2,A}/t_{1/2,H}$)**
Mouse	Male	5.8[a]	1,050[b]	0.0055
	Female	4.5[c]		0.0043
Rat	Male	4.8[d]		0.0046
	Female	5.7[e]		0.0054

[a]Terminal serum half-life of combined doses for male mice from [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6579272"].
[b]Mean serum elimination half-life for humans (combined sexes) from [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6781357"].
[c]Terminal serum half-life of combined doses for female mice from [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6579272"].
[d]Geometric mean of terminal serum half-lives ($t_{1/2,\beta}$) measured after all oral and i.v. doses for male rats from [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"] and [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5387170"].
[e]Mean of terminal serum half-lives ($t_{1/2,\beta}$) measured after oral and i.v. doses for female rats from [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"].

DAF = dosimetric adjustment factor; i.v. = intravenous; $t_{1/2}$ = half-life.

Where modeling was feasible, the estimated BMDLs were identified as PODs (summarized in [REF _Ref55818467 \h]). Further details, including the modeling output and graphical results for the model selected for each endpoint, can be found in HAWC and are discussed in Appendix F. Where dose-response modeling was not feasible, NOAELs or LOAELs were identified (summarized in [REF _Ref55818467 \h]).

Table [SEQ Table * ARABIC]. PODs Considered for Deriving the Subchronic RfD for K^+PFBS (CASRN 29420-49-3)			
Endpoint/Reference	**Species/Life Stage—Sex**	**POD (HED)[a] (mg/kg-d)**	**Comments[‡]**
Thyroid effects			
Total T_4—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"]	Mouse/P_0—female	$BMDL_{1SD}$ = 0.093	Adequate model fit
Free T_4—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"]	Mouse/P_0—female	NOAEL = 0.21	No models provided adequate statistical or visual fit to mean responses

Table [SEQ Table * ARABIC]. PODs Considered for Deriving the Subchronic RfD for K^+PFBS (CASRN 29420-49-3)			
Endpoint/Reference	**Species/Life Stage—Sex**	**POD (HED)[a] (mg/kg-d)**	**Comments[‡]**
TSH—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"]	Mouse/P_0—female	NOAEL = 0.21	No models provided adequate statistical or visual fit to mean responses
Total T_4 PND 1 (fetal *n*)[b]—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"]	Mouse/F_1—female	NOAEL = 0.21	No models provided adequate fit to the data, specifically variance
Total T_4 PND 1 (litter *n*)[b]—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"]	Mouse/F_1—female	$BMDL_{0.5SD}$ = 0.095 ($BMDL_{1SD}$ = 0.25)	Adequate model fit
Total T_4 PND 30—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"]	Mouse/F_1—female	NOAEL = 0.21	No models provided adequate statistical or visual fit to mean responses
Total T_4 PND 60—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"]	Mouse/F_1—female	NOAEL = 0.21	No models provided adequate fit to the data, specifically variance

Table [SEQ Table * ARABIC]. PODs Considered for Deriving the Subchronic RfD for K^+PFBS (CASRN 29420-49-3)			
Endpoint/Reference	**Species/Life Stage—Sex**	**POD (HED)[a] (mg/kg-d)**	**Comments[‡]**
TSH PND 30—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"]	Mouse/F_1—female	NOAEL = 0.21	No models provided adequate statistical or visual fit to mean responses
Total T_4—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5400978"]	Rat—male	LOAEL = 0.29	No models provided adequate statistical or visual fit to mean responses
	Rat—female	$BMDL_{1SD}$ = 0.037	Adequate model fit
Free T_4—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5400978"]	Rat—male	LOAEL = 0.34	No models provided adequate statistical or visual fit to mean responses
	Rat—female	$BMDL_{1SD}$ = 0.027	Adequate model fit
Developmental effects			
Eyes opening (fetal *n*)[b]—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"]	Mouse/F_1—female	NOAEL = 0.21	No models provided adequate fit to the data, specifically variance
Eyes opening (litter *n*)[b]—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"]	Mouse/F_1—female	$BMDL_{0.5SD}$ = 0.073 ($BMDL_{1SD}$ = 0.16)	Adequate model fit

Table [SEQ Table * ARABIC]. PODs Considered for Deriving the Subchronic RfD for K^+PFBS (CASRN 29420-49-3)			
Endpoint/Reference	**Species/Life Stage—Sex**	**POD (HED)[a] (mg/kg-d)**	**Comments[‡]**
Vaginal opening (fetal *n*)[b]—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"]	Mouse/F_1—female	$BMDL_{0.5SD}$ = 0.15 ($BMDL_{1SD}$ = 0.35)	Adequate model fit
Vaginal opening (litter *n*)[b]—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"]	Mouse/F_1—female	$BMDL_{0.5SD}$ = 0.094 ($BMDL_{1SD}$ = 0.22)	Adequate model fit
First estrous (fetal *n*)[b]—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"]	Mouse/F_1—female	NOAEL = 0.21	No models provided adequate statistical or visual fit to mean responses
First estrous (litter *n*)[b]—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"]	Mouse/F_1—female	NOAEL = 0.21	No models provided adequate statistical or visual fit to mean responses
Kidney effects			
Kidney histopathology—papillary epithelial tubular/ductal hyperplasia—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578546"]	Rat—male	$BMDL_{10}$ = 0.49	Adequate model fit
	Rat—female	$BMDL_{10}$ = 0.30	Adequate model fit
Kidney histopathology—papillary epithelial tubular/ductal hyperplasia—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578545"]	Rat/P_0—male	$BMDL_{10}$ = 0.35	Adequate model fit
	Rat/P_0—female	$BMDL_{10}$ = 0.27	Adequate model fit

Table [SEQ Table * ARABIC]. PODs Considered for Deriving the Subchronic RfD for K^+PFBS (CASRN 29420-49-3)			
Endpoint/Reference	**Species/Life Stage—Sex**	**POD (HED)[a] (mg/kg-d)**	**Comments[‡]**
Kidney histopathology—papillary epithelial tubular/ductal hyperplasia—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578545"]	Rat/F_1—male	$BMDL_{10}$ = 0.78	Adequate model fit
	Rat/F_1—female	$BMDL_{10}$ = 0.48	Adequate model fit

[a]Following [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=752972"] and [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=2520260"] guidance, animal doses from candidate principal studies were converted to HEDs by applying a DAF, where HED = dose × DAF.
[b]Fetal endpoints from [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"] were modeled alternatively using dose-group sizes based either on total number of fetuses or dams. Given that [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"] seems not to have used the litter as the statistical unit of analysis, it is unclear whether the study-reported standard errors pertain to litters or fetuses. Alternatively, modeling fetal endpoints using litter *n* or fetal *n* provides two modeling results that bracket the "true" variance among all fetuses in a dose group (i.e., using the fetal *n* will underestimate the true variance while using the litter *n* will overestimate the true variance). Individual animal data were requested from study authors but were unable to be obtained.
[‡]BMD modeling methods and links to modeling inputs and results in HAWC are found in Appendix F. HAWC visualization: [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-candidate-pods-subchronic-and-chronic-rfd/"].

$BMDL_{0.5SD}$ = benchmark dose lower confidence limit for 0.5 SD change from the control; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; $BMDL_{1SD}$ = benchmark dose lower confidence limit for 1 SD change from the control; DAF = dosimetric adjustment factor; HAWC = Health Assessment Workspace Collaborative; HED = human equivalent dose; K^+PFBS = potassium perfluorobutane sulfonate; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; PND = postnatal day; POD = point of departure; RfD = oral reference dose; SD = standard deviation; T_4 = thyroxine; TSH = thyroid stimulating hormone.

6.1.1.3 Considerations in Selecting the Critical Effect for Deriving Oral Reference Doses

The evidence for the thyroid, developmental, and kidney effect domains *support a hazard* via the oral exposure route (see [REF _Ref55818151 \h]). However, there are qualitative and quantitative differences in the strength of evidence between these effect domains (see [REF _Ref55818467 \h]). PFBS-induced perturbation of the thyroid was consistently observed across two species, sexes, life stages, and exposure durations in two independent, high-confidence studies. These perturbations involved a coherent pattern of hormonal changes with similar sensitivity in the POD ranges across life stages (e.g., maternal and PND 1/newborn $BMDL_{05}$s of 0.093 and 0.095 mg/kg-day, respectively). Developmental effects (e.g., delayed eyes opening, vaginal opening, or first estrous) were observed in mouse litters in which decrements in thyroid hormone occurred and with similar sensitivity in the ranges of POD estimates (i.e., 0.073−0.21 mg/kg-day) [ADDIN EN.CITE <EndNote><Cite><Author>Feng</Author><Year>2017</Year><RecNum>1031</RecNum><IDText>3856465</IDText><DisplayText>(Feng et al., 2017)</DisplayText><record><rec-number>1031</rec-number><foreign-keys><key app="EN" db-

id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1031</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Feng, X.</author><author>Cao, X.</author><author>Zhao, S.</author><author>Wang, X.</author><author>Hua, X.</author><author>Chen, L.</author><author>Chen, L.</author></authors></contributors><titles><title>Exposure of pregnant mice to perfluorobutanesulfonate causes hypothyroxinemia and developmental abnormalities in female offspring</title><secondary-title>Toxicological Sciences</secondary-title><alt-title>Toxicol Sci</alt-title><short-title>Toxicological Sciences</short-title></titles><periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></periodical><alt-periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></alt-periodical><pages>409-419</pages><volume>155</volume><number>2</number><dates><year>2017</year></dates><isbn>ISSN 1096-6080
EISSN 1096-0929</isbn><accession-num>27803384</accession-num><label>3856465</label><urls><related-urls><url>http://dx.doi.org/10.1093/toxsci/kfw219</url></related-urls></urls><electronic-resource-num>10.1093/toxsci/kfw219</electronic-resource-num><language>English</language></record></Cite></EndNote>]. However, these developmental effects have been reported in a single study and species (mouse). Kidney effects in adult animals [ADDIN EN.CITE ADDIN EN.CITE.DATA] were observed in adult or developing rats across high- or medium-confidence gavage studies of various duration; however, were less sensitive at 0.27 mg/kg-day and above.

In deriving a subchronic RfD, both the [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"] and [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5400978"] studies were considered as potential principal studies because of the observed sensitivity of thyroid hormone decrements. However, the biological significance of hypothyroxinemia (i.e., decreased T_4) in adult euthyroid animals, absent additional signs of overt thyroid toxicity (e.g., reflex increase in TSH and/or alterations in tissue weight or histology), is unclear; therefore, the thyroid effects from the [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5400978"] rat study were not selected as a critical effect. The gestational exposure study in mice was selected as the principal study for deriving the subchronic RfD based on thyroid effects. The gestational exposure study conducted by [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"] reported administration of K^+PFBS by gavage in ICR mice (10/dose) from GDs 1 to 20. This study was of good quality (i.e., high confidence) with adequate reporting and consideration for appropriate study design, methods, and conduct (click to see [HYPERLINK "https://hawcprd.epa.gov/rob/study/100000968/"] in HAWC). [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"] reported statistically significantly decreased total T_3, total T_4, and free T_4, as well as increased TSH in dams and offspring (increased TSH PND 30 only) gestationally exposed to PFBS.

The critical effect from the [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"] study was decreased serum total thyroxine (T_4) in newborn (PND 1) mice. T_4 and T_3 are essential for

normal growth of developing offspring across animal species [for review see [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=2344788"]]. And, previous studies have shown that exposure to other PFAS during pregnancy results in lower T_4 and T_3 levels in pregnant women and fetuses or neonates [ADDIN EN.CITE ADDIN EN.CITE.DATA]. The selection of total T_4 as the critical effect is based on a number of key considerations (see below) that account for cross-species correlations in thyroid physiology and hormone dynamics particularly within the context of a developmental life stage.

A key consideration for selecting total T_4 is that this represents the aggregate of potential thyroid endocrine signaling (i.e., free T_4 + protein bound T_4) at any given time. In humans, FT_4 represents approximately 0.03% of circulating hormone, indicating that as much as 99.97% of all T_4 is protein bound (e.g., albumin; TBG). Although T_3 is the active hormone form in respondent somatic tissues, the formation of T_3 is contingent upon the deiodination of free T_4. A critical consideration in pregnant females is that T_4, not T_3, is the thyroid hormone that crosses the placenta of humans and rodents. Although free T_4 might be considered a suitable measure of thyroid hormone status in nondevelopmental (e.g., adult) life stages, there are some important factors associated with maintenance of the microenvironment for developing offspring in utero that supports using total T_4 as the critical effect. A tightly regulated transfer of maternal thyroid hormone to a fetus is paramount to proper development of multiple tissues and organ systems (e.g., nervous system), especially during the early trimesters. The placenta has transporters and deiodinases that collectively act as a gatekeeper to maintain an optimal T_4 microenvironment in the fetal compartment [ADDIN EN.CITE ADDIN EN.CITE.DATA]. For example, deiodinase 3 (D3) is highly expressed in human uterus, placenta, and amniotic membrane, where it serves a critical role of regulating thyroid hormone transfer to the fetus through the deiodination of T_4 to transcriptionally inactive reverse triiodothyronine (rT_3) or T_3 to inactive 3,5-diiodo-L-thyronine (T_2). Similarly, [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=4616561"] showed that D3 is highly expressed in the rodent uterus and is highly induced during pregnancy. Further, the *Dio3* gene that encodes D3 has been shown to be imprinted in the mouse [ADDIN EN.CITE
<EndNote><Cite><Author>Hernandez</Author><Year>2002</Year><RecNum>842</RecNum><IDText>4616555</IDText><DisplayText>(Hernandez et al., 2002)</DisplayText><record><rec-number>842</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">842</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Hernandez, A., Fiering, S.</author><author>Martinez, E.</author><author>Galton,,VA</author><author>St Germain, D.</author></authors></contributors><titles><title>The gene locus encoding iodothyronine deiodinase type 3 (Dio3) is imprinted in the fetus and expresses antisense transcripts</title><secondary-title>Endocrinology</secondary-title><alt-title>Endocrinology</alt-title><short-title>Endocrinology</short-title></titles><periodical><full-title>Endocrinology</full-title><abbr-1>Endocrinology</abbr-1></periodical><alt-periodical><full-title>Endocrinology</full-title><abbr-1>Endocrinology</abbr-1></alt-periodical><pages>4483-4486</pages><volume>134</volume><number>11</number><dates><year>2002</year></dates><isbn>ISSN 0013-7227
EISSN 1945-7170</isbn><accession-num>12399446</accession-num><label>4616555</label><urls></urls><language>English</language></record></Cite></

EndNote>], suggesting a pivotal role for this specific deiodinase in the mouse as well. Indeed, the human and rodent placenta have been shown to be similarly permeable to T_4 and T_3 [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Due to placental barrier functionality, free T_4 levels in a pregnant dam might not be entirely representative of actual T_4 status in a developing fetus. Further, the American Thyroid Association published a guidelines document in 2017 in which they stated: "Current uncertainty around FT_4 estimates in pregnancy has led some to question the wisdom of relying on any FT_4 immunoassays during pregnancy. In contrast, measurement of TT_4 and the calculated FT_4 index do show the expected inverse relationship with serum TSH. This finding suggests that TT_4 measurements may be superior to immunoassay measurement of FT_4 measurements in pregnant women" [ADDIN EN.CITE <EndNote><Cite><Author>Alexander</Author><Year>2017</Year><RecNum>1021</RecNum><IDText>3589983</IDText><DisplayText>(Alexander et al., 2017)</DisplayText><record><rec-number>1021</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1021</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Alexander, E. K.</author><author>Pearce, E. N.</author><author>Brent, G. A.</author><author>Brown, R. S.</author><author>Chen, H.</author><author>Dosiou, C.</author><author>Grobman, W.</author><author>Laurberg, P.</author><author>Lazarus, J. H.</author><author>Mandel, S. J.</author><author>Peeters, R.</author><author>Sullivan, S.</author></authors></contributors><titles><title>2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum</title><secondary-title>Thyroid</secondary-title><alt-title>Thyroid</alt-title><short-title>Thyroid</short-title></titles><periodical><full-title>Thyroid</full-title><abbr-1>Thyroid</abbr-1></periodical><alt-periodical><full-title>Thyroid</full-title><abbr-1>Thyroid</abbr-1></alt-periodical><pages>315-389</pages><volume>27</volume><number>3</number><dates><year>2017</year></dates><isbn>ISSN 1050-7256
EISSN 1557-9077</isbn><accession-num>28056690</accession-num><label>3589983</label><urls><related-urls><url>http://dx.doi.org/10.1089/thy.2016.0457</url></related-urls></urls><electronic-resource-num>10.1089/thy.2016.0457</electronic-resource-num><language>English</language></record></Cite></EndNote>]. Thus, decreased total T_4 in offspring (and dams during pregnancy/at delivery) is expected to be more representative of PFBS-mediated thyroid effects and potentially associative developmental effects.

There are some differences in HPT development and functional maturation and regulation during early life stages (e.g., timing of in utero and early postnatal thyroid development) between humans and rodents [for a comprehensive overview see [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6395874"]]. Human thyroid development occurs in three phases in utero which entails initial development of the gland between Embryonic Day 10 to Gestational Week 11 (Phase I), maturation of the fetal thyroid system from Gestational Weeks 11–35 (Phase II), and further refinement of hypothalamic-pituitary-thyroid axis functionality during the latter portion of gestation up to approximately 4 weeks into the postnatal period (Phase III) [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Importantly, in utero development of the rodent thyroid gland occurs in the same phases and order as humans, the difference being that rodents are essentially born during Phase II, with Phase III occurring almost exclusively postnatally; whereas in humans, Phase III is

well underway in utero and completes postnatally. Accordingly, rodent neurodevelopment in the early postnatal phase is analogous to the third trimester of human development in utero [ADDIN EN.CITE
<EndNote><Cite><Author>Gilbert</Author><Year>2012</Year><RecNum>988</RecNum><IDText>1609642</IDText><DisplayText>(Gilbert et al., 2012)</DisplayText><record><rec-number>988</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">988</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Gilbert, M. E.</author><author>Rovet, J.</author><author>Chen, Z.</author><author>Koibuchi, N.</author></authors></contributors><titles><title>Developmental thyroid hormone disruption: prevalence, environmental contaminants and neurodevelopmental consequences</title><secondary-title>NeuroToxicology</secondary-title><alt-title>Neurotoxicology</alt-title><short-title>NeuroToxicology</short-title></titles><periodical><full-title>NeuroToxicology</full-title><abbr-1>Neurotoxicology</abbr-1></periodical><alt-periodical><full-title>NeuroToxicology</full-title><abbr-1>Neurotoxicology</abbr-1></alt-periodical><pages>842-852</pages><volume>33</volume><number>4</number><dates><year>2012</year></dates><isbn>ISSN 0161-813X
EISSN 1872-9711</isbn><accession-num>22138353</accession-num><label>1609642</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.neuro.2011.11.005</url></related-urls></urls><electronic-resource-num>10.1016/j.neuro.2011.11.005</electronic-resource-num><language>English</language></record></Cite></EndNote>]. Further, fetal development of rodents in utero is entirely dependent on maternal thyroid hormone until approximately GD 17−18, whereas in humans, fetal development transitions from complete reliance on maternal thyroid hormone during the first trimester (i.e., thyroid development Phase I) to a mix of fetal thyroid hormone synthesis and maternal transplacental hormone transfer beginning in the second trimester (i.e., thyroid development Phase II) through the in utero portion of Phase III [ADDIN EN.CITE
<EndNote><Cite><Author>Fisher</Author><Year>1981</Year><RecNum>991</RecNum><IDText>2149222</IDText><DisplayText>(Fisher and Klein, 1981)</DisplayText><record><rec-number>991</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">991</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Fisher, D. A.</author><author>Klein, A. H.</author></authors></contributors><titles><title>Thyroid development and disorders of thyroid function in the newborn</title><secondary-title>New England Journal of Medicine</secondary-title><alt-title>N Engl J Med</alt-title><short-title>New England Journal of Medicine</short-title></titles><periodical><full-title>New England Journal of Medicine</full-title><abbr-1>N Engl J Med</abbr-1></periodical><alt-periodical><full-title>New England Journal of Medicine</full-title><abbr-1>N Engl J Med</abbr-1></alt-periodical><pages>702-712</pages><volume>304</volume><number>12</number><dates><year>1981</year></dates><isbn>ISSN 0028-4793
EISSN 1533-4406</isbn><accession-num>6258072</accession-num><label>2149222</label><work-type>Review</work-type><urls><related-urls><url>http://dx.doi.org/10.1056/NEJM198103193041205</url></related-urls></urls><electronic-resource-num>10.1056/nejm198103193041205</electronic-resource-num><language>English</language></record></Cite></EndNote>].

Within the context of early developmental life stages, there are several commonalities in HPT dynamics between humans and rodents such as similar profiles of (1) thyroid hormone binding proteins, (2) hormone functional reserve, and (3) placental deiodinase. For example, two carrier proteins—thyroid binding globulin (TBG) and transthyretin (TTR)—are primarily responsible for storage and transit of T_4 in mammals [ADDIN EN.CITE <EndNote><Cite><Author>Rabah</Author><Year>2019</Year><RecNum>1175</RecNum><IDText>6556922</IDText><DisplayText>(Rabah et al., 2019)</DisplayText><record><rec-number>1175</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1175</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Rabah, S. A.</author><author>Gowan, I. L.</author><author>Pagnin, M.</author><author>Osman, N.</author><author>Richardson, S. J.</author></authors></contributors><titles><title>Thyroid Hormone Distributor Proteins During Development in Vertebrates</title><secondary-title>Frontiers in Endocrinology</secondary-title><alt-title>Front Endocrinol (Lausanne)</alt-title><short-title>Frontiers in Endocrinology</short-title></titles><periodical><full-title>Frontiers in Endocrinology</full-title><abbr-1>Front Endocrinol (Lausanne)</abbr-1></periodical><alt-periodical><full-title>Frontiers in Endocrinology</full-title><abbr-1>Front Endocrinol (Lausanne)</abbr-1></alt-periodical><pages>506</pages><volume>10</volume><dates><year>2019</year></dates><isbn>ISSN 1664-2392
EISSN 1664-2392</isbn><accession-num>31440205</accession-num><label>6556922</label><work-type>Review</work-type><urls><related-urls><url>http://dx.doi.org/10.3389/fendo.2019.00506</url></related-urls></urls><electronic-resource-num>10.3389/fendo.2019.00506</electronic-resource-num><language>English</language></record></Cite></EndNote>]. TBG is the primary carrier of T_4 in humans across all life stages [ADDIN EN.CITE <EndNote><Cite><Author>Savu</Author><Year>1991</Year><RecNum>967</RecNum><IDText>4623189</IDText><DisplayText>(Savu et al., 1991)</DisplayText><record><rec-number>967</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">967</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Savu, L.</author><author>Vranckx, R.</author><author>Rouaze-Romet, M.</author><author>Maya, M.</author><author>Nunez, E. A.</author><author>Tréton, J.</author><author>Flink, I. L.</author></authors></contributors><titles><title>A senescence up-regulated protein: the rat thyroxine-binding globulin (TBG)</title><secondary-title>Biochimica et Biophysica Acta</secondary-title><alt-title>Biochim Biophys Acta</alt-title><short-title>Biochimica et Biophysica Acta</short-title></titles><periodical><full-title>Biochimica et Biophysica Acta</full-title><abbr-1>Biochim Biophys Acta</abbr-1></periodical><alt-periodical><full-title>Biochimica et Biophysica Acta</full-title><abbr-1>Biochim Biophys Acta</abbr-1></alt-periodical><pages>19-22</pages><volume>1097</volume><number>1</number><dates><year>1991</year></dates><isbn>ISSN 0006-3002
EISSN 1878-2434</isbn><accession-num>1907201</accession-num><label>4623189</label><urls></urls><language>English</language></record></Cite></EndNote>]. Importantly, in fetal and infant rats, TBG is also the primary carrier of T_4 [ADDIN EN.CITE <EndNote><Cite><Author>Savu</Author><Year>1989</Year><RecNum>966</RecNum><IDText>4623190</IDText><DisplayText>(Savu et al., 1989)</DisplayText><record><rec-

number>966</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">966</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Savu, L.</author><author>Vranckx, R.</author><author>Maya, M.</author><author>Gripois, D.</author><author>Blouquit, M. F.</author><author>Nunez, E. A.</author></authors></contributors><titles><title>Thyroxine-binding globulin and thyroxine-binding prealbumin in hypothyroid and hyperthyroid developing rats</title><secondary-title>Biochimica et Biophysica Acta</secondary-title><alt-title>Biochim Biophys Acta</alt-title><short-title>Biochimica et Biophysica Acta</short-title></titles><periodical><full-title>Biochimica et Biophysica Acta</full-title><abbr-1>Biochim Biophys Acta</abbr-1></periodical><alt-periodical><full-title>Biochimica et Biophysica Acta</full-title><abbr-1>Biochim Biophys Acta</abbr-1></alt-periodical><pages>379-384</pages><volume>992</volume><number>3</number><dates><year>1989</year></dates><isbn>ISSN 0006-3002
EISSN 1878-2434</isbn><accession-num>2505856</accession-num><label>4623190</label><urls></urls><language>English</language></record></Cite></EndNote>]. As rats transition to adulthood, TTR takes over as the primary carrier of T_4. In addition, as a relatively highly abundant carrier protein, albumin also plays a role in thyroid hormone binding and transit in humans and rodents; however, the relative affinity for binding is lower than either TBG or TTR.

Life-stage-specific differences in thyroid hormone reserve capacity between adults and neonates have been noted. On average, intrathyroidal thyroglobulin stores in adults are on the order of months, whereas in neonates the functional reserve is approximated at less than 1 day [ADDIN EN.CITE ADDIN EN.CITE.DATA]. This suggests that the adult thyroid has compensatory abilities not present in early life stages, making fetal/neonatal populations particularly sensitive to perturbations in thyroid hormone economy (e.g., hypothyroxinemia). And although the timing of thyroid development can vary between species [ADDIN EN.CITE <EndNote><Cite><Author>Forhead</Author><Year>2014</Year><RecNum>1193</RecNum><IDText>2344788</IDText><DisplayText>(Forhead and Fowden, 2014)</DisplayText><record><rec-number>1193</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1193</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Forhead, A. J.</author><author>Fowden, A. L.</author></authors></contributors><titles><title>Thyroid hormones in fetal growth and prepartum maturation</title><secondary-title>Journal of Endocrinology</secondary-title><alt-title>J Endocrinol</alt-title><short-title>Journal of Endocrinology</short-title></titles><periodical><full-title>Journal of Endocrinology</full-title><abbr-1>J Endocrinol</abbr-1></periodical><alt-periodical><full-title>Journal of Endocrinology</full-title><abbr-1>J Endocrinol</abbr-1></alt-periodical><pages>R87-R103</pages><volume>221</volume><number>3</number><dates><year>2014</year></dates><isbn>ISSN 0022-0795
EISSN 1479-6805</isbn><accession-num>24648121</accession-num><label>2344788</label><work-type>Review</work-type><urls><related-urls><url>http://dx.doi.org/10.1530/JOE-14-0025</url></related-urls></urls><electronic-resource-num>10.1530/joe-14-0025</electronic-resource-num><language>English</language></record></Cite></EndNote>], the dynamic reserve capacity of T_4 between humans and rodents near birth and in early postpartum might not be significantly different. For example, human neonates have a serum half-life of T_4 of

approximately 3 days [ADDIN EN.CITE <EndNote><Cite><Author>Vulsma</Author><Year>1989</Year><RecNum>331</RecNum><IDText>2139289</IDText><DisplayText>(Vulsma et al., 1989)</DisplayText><record><rec-number>331</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604955473">331</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Vulsma, T.</author><author>Gons, M. H.</author><author>de Vijlder, J. J.</author></authors></contributors><titles><title>Maternal-fetal transfer of thyroxine in congenital hypothyroidism due to a total organification defect or thyroid agenesis</title><secondary-title>New England Journal of Medicine</secondary-title><alt-title>N Engl J Med</alt-title><short-title>New England Journal of Medicine</short-title></titles><periodical><full-title>New England Journal of Medicine</full-title><abbr-1>N Engl J Med</abbr-1></periodical><alt-periodical><full-title>New England Journal of Medicine</full-title><abbr-1>N Engl J Med</abbr-1></alt-periodical><pages>13-16</pages><volume>321</volume><number>1</number><dates><year>1989</year></dates><isbn>ISSN 0028-4793
EISSN 1533-4406</isbn><accession-num>2733742</accession-num><label>2139289</label><urls><related-urls><url>http://dx.doi.org/10.1056/NEJM198907063210103</url></related-urls></urls><electronic-resource-num>10.1056/nejm198907063210103</electronic-resource-num><language>English</language></record></Cite></EndNote>], and thyroid tissue stores of T_4 are estimated to be less than 1 day [ADDIN EN.CITE <EndNote><Cite><Author>van den Hove</Author><Year>1999</Year><RecNum>968</RecNum><IDText>16478</IDText><DisplayText>(van den Hove et al., 1999)</DisplayText><record><rec-number>968</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">968</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>van den Hove, M. F.</author><author>Beckers, C.</author><author>Devlieger, H.</author><author>de Zegher, F.</author><author>De Nayer, P.</author></authors></contributors><titles><title>Hormone synthesis and storage in the thyroid of human preterm and term newborns: effect of thyroxine treatment</title><secondary-title>Biochimie</secondary-title><alt-title>Biochimie</alt-title><short-title>Biochimie</short-title></titles><periodical><full-title>Biochimie</full-title><abbr-1>Biochimie</abbr-1></periodical><alt-periodical><full-title>Biochimie</full-title><abbr-1>Biochimie</abbr-1></alt-periodical><pages>563-570</pages><volume>81</volume><number>5</number><dates><year>1999</year></dates><isbn>ISSN 0300-9084
EISSN 1638-6183</isbn><accession-num>10403191</accession-num><label>16478</label><work-type>Review</work-type><urls></urls><language>English</language></record></Cite></EndNote>]. Because the developing rodent thyroid does not begin producing its own hormone until late in gestation (≥GD 17), newborn rodent T_4 levels are primarily a reflection of transplacentally translocated maternal hormone; and adult rats have been shown to have a serum T_4 half-life of 0.5–1 day [ADDIN EN.CITE <EndNote><Cite><Author>Choksi</Author><Year>2003</Year><RecNum>3</RecNum><IDText>5202606</IDText><DisplayText>(Choksi et al., 2003)</DisplayText><record><rec-number>3</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604955316">3</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Choksi,

N. Y.</author><author>Jahnke, G. D.</author><author>St Hilaire, C.</author><author>Shelby, M.</author></authors></contributors><titles><title>Role of thyroid hormones in human and laboratory animal reproductive health</title><secondary-title>Birth Defects Research, Part B: Developmental and Reproductive Toxicology</secondary-title><alt-title>Birth Defects Res B Dev Reprod Toxicol</alt-title><short-title>Birth Defects Research, Part B: Developmental and Reproductive Toxicology</short-title></titles><periodical><full-title>Birth Defects Research, Part B: Developmental and Reproductive Toxicology</full-title><abbr-1>Birth Defects Res B Dev Reprod Toxicol</abbr-1></periodical><alt-periodical><full-title>Birth Defects Research, Part B: Developmental and Reproductive Toxicology</full-title><abbr-1>Birth Defects Res B Dev Reprod Toxicol</abbr-1></alt-periodical><pages>479–491</pages><volume>68</volume><number>6</number><dates><year>2003</year></dates><isbn>ISSN 1542-9733
EISSN 1542-9741</isbn><accession-num>14745982</accession-num><label>5202606</label><work-type>Review</work-type><urls><related-urls><url>http://dx.doi.org/10.1002/bdrb.10045</url></related-urls></urls><electronic-resource-num>10.1002/bdrb.10045</electronic-resource-num><language>English</language></record></Cite></EndNote>]. For this reason, significant differences in functional thyroid reserve capacity between human and rodent neonates are not anticipated.

Accounting for the information presented above, the subchronic RfD, based on the $BMDL_{0.5SD}$ (HED) of 0.095 mg/kg-day for decreased serum total T_4 in newborn (PND 1) mice, is derived as follows:

Subchronic RfD for K^+PFBS	=	$BMDL_{0.5SD}$ (HED) ÷ UF_C
	=	0.095 mg/kg-day ÷ 100
	=	0.00095mg/kg-day
	=	**1×10^{-3} mg/kg-day**

[REF _Ref55817965 \h] summarizes the uncertainty factors for the subchronic RfD for K^+PFBS based on effects in the thyroid.

Table [SEQ Table * ARABIC]. Uncertainty Factors for the Subchronic RfD for Thyroid Effects for K^+PFBS (CASRN 29420-49-3)		
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 mice and humans following oral K^+PFBS/PFBS exposure. Some aspects of the cross-species extrapolation of toxicokinetic and toxicodynamic processes have been accounted for by calculating an HED by applying a DAF as outlined in the U.S. EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2011</Year><RecNum>1311</RecNum><IDText>752972</IDText><DisplayText>(U.S. EPA, 2011b)</DisplayText><record><rec-number>1311</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1311</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Recommended use of body weight 3/4 as the default method in derivation of the oral reference dose</title></titles><pages>1-50</pages><dates><year>2011</year></dates><pub-location>Washington, DC</pub-location><publisher>U.S. Environmental Protection Agency, Risk Assessment Forum, Office of the Science Advisor</publisher><isbn>EPA/100/R-11/0001</isbn><label>752972</label><urls><related-urls><url>https://www.epa.gov/sites/production/files/2013-09/documents/recommended-use-of-bw34.pdf</url></related-urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>]. However, some residual uncertainty remains in the relative cross-species sensitivity in toxicodynamics (e.g., thyroid signaling). Thus, in the absence of chemical-specific data to quantify these uncertainties, U.S. EPA's guidance recommends use of a UF_A of 3.

Table [SEQ Table * ARABIC]. Uncertainty Factors for the Subchronic RfD for Thyroid Effects for K^+PFBS (CASRN 29420-49-3)

UF	Value	Justification
UF_D	3	A UF_D of 3 is applied due to database deficiencies. The oral exposure database contains multiple short-term and subchronic-duration toxicity studies of laboratory animals [ADDIN EN.CITE ADDIN EN.CITE.DATA], a two-generation reproductive toxicity study in rats [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1044</RecNum><IDText>1578545</IDText><DisplayText>(Lieder et al., 2009b)</DisplayText><record><rec-number>1044</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1044</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lieder, P. H.</author><author>York, R. G.</author><author>Hakes, D. C.</author><author>Chang, S. C.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>A two-generation oral gavage reproduction study with potassium perfluorobutanesulfonate (K+PFBS) in Sprague Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>33-45</pages><volume>259</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>19428941</accession-num><label>1578545</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2009.01.027</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2009.01.027</electronic-resource-num><language>English</language></record></Cite></EndNote>], and multiple developmental toxicity studies in mice and rats [ADDIN EN.CITE ADDIN EN.CITE.DATA]. However, the observation of decreased thyroid hormone is known to be a crucial element during developmental life stages, particularly for neurodevelopment, and the database is limited by the lack of developmental neurotoxicity studies. In addition, because other health effect domains such as immunotoxicity and mammary gland development are effects of increasing concern across several members of the larger PFAS family [ADDIN EN.CITE ADDIN EN.CITE.DATA], the lack of studies evaluating these outcomes following PFBS exposure is a limitation in the database.
UF_H	10	A UF_H of 10 is applied to account for interindividual variability in the human populations because of both intrinsic (toxicokinetic, toxicodynamic, genetic, life stage, and health status) and extrinsic (life style) factors that can influence the response to dose. In the absence of chemical-specific data to quantify this variability in the [SEQ CHAPTER \h \r 1]toxicokinetics and toxicodynamics of K^+PFBS/PFBS in humans, U.S. EPA recommends using a UF_H of 10.
UF_L	1	A UF_L of 1 is applied for LOAEL-to-NOAEL extrapolation because the POD is a BMDL and the BMR was selected based on evidence that it represented a minimal biologically significant response level in susceptible populations such as developing offspring.

Table [SEQ Table * ARABIC]. Uncertainty Factors for the Subchronic RfD for Thyroid Effects for K^+PFBS (CASRN 29420-49-3)		
UF	**Value**	**Justification**
UF_S	1	A UF_S of 1 is applied because the POD comes from a developmental study in mice. The developmental period is recognized as a susceptible life stage in which exposure during certain time windows (e.g., gestational) is more relevant to the induction of developmental effects than lifetime exposure [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>1991</Year><RecNum>938</RecNum><IDText>732120</IDText><DisplayText>(U.S. EPA, 1991a)</DisplayText><record><rec-number>938</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">938</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Guidelines for developmental toxicity risk assessment</title><secondary-title>Federal Register</secondary-title><alt-title>Fed. Reg.</alt-title><short-title>Federal Register</short-title></titles><periodical><full-title>Federal Register</full-title><abbr-1>Fed. Reg.</abbr-1></periodical><alt-periodical><full-title>Federal Register</full-title><abbr-1>Fed. Reg.</abbr-1></alt-periodical><pages>63798-63826</pages><volume>56</volume><number>234</number><dates><year>1991</year></dates><isbn>ISSN 0097-6326
EISSN 2167-2520</isbn><label>732120</label><urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>].
UF_C	100	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$

BMDL = benchmark dose lower confidence limit; BMR = benchmark response; DAF = dosimetric adjustment factor; HED = human equivalent dose; K^+PFBS = potassium perfluorobutane sulfonate; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; PFAS = per- and polyfluoroalkyl substances; PFBS = perfluorobutane sulfonic acid; POD = point of departure; RfD = oral 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 = subchronic-to-chronic uncertainty factor.

The data for K^+PFBS can be used to derive a subchronic RfD for the free acid (PFBS), as K^+PFBS is fully dissociated in water at the environmental pH range of 4–9 [ADDIN EN.CITE <EndNote><Cite><Author>NICNAS</Author><Year>2005</Year><RecNum>1306</RecNum><IDText>1784741</IDText><DisplayText>(NICNAS, 2005)</DisplayText><record><rec-number>1306</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1306</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NICNAS,</author></authors></contributors><titles><title>Existing chemical hazard assessment report. Potassium perfluorbutane sulfonate</title></titles><dates><year>2005</year></dates><pub-location>Canberra, Australia</pub-location><publisher>Commonwealth of Australia, Australian Government Publishing</publisher><label>1784741</label><urls><related-urls><url>https://web.archive.org/web/20200503121653/http://www.nicnas.gov.au/__data/assets/pdf_file/0004/4927/Potassium_Perfluorobutane_Sulfonate_PDF.pdf</url></related-urls></urls><language>English</language><modified-date>National Industrial Chemicals Notification and Assessment Scheme</modified-date></record></Cite></EndNote>]. To calculate the subchronic RfD for the free acid, the subchronic RfD for the potassium salt is

adjusted to compensate for differences in MW between K^+PFBS (338.19) and PFBS (300.10). The subchronic RfD for PFBS (free acid) is calculated as follows:

Subchronic RfD	=	RfD for K^+PFBS salt × (MW free acid ÷ MW salt)
for PFBS (free acid)	=	0.00095 mg/kg-day × (300.10 ÷ 338.19)
	=	0.00095 mg/kg-day × (0.89)
	=	0.00085 mg/kg-day
	=	**9×10^{-4} mg/kg-day**

Confidence in the subchronic RfD for PFBS and K^+PFBS for thyroid effects is medium, as explained in [REF _Ref55818532 \h].

Table [SEQ Table * ARABIC]. Confidence Descriptors for the Subchronic RfD for PFBS (CASRN 375-73-5) and the Related Compound K^+PFBS (CASRN 29420-49-3)

Confidence Categories	Designation	Discussion
Confidence in study	H	Confidence in the principal study is high because the overall study design, performance, and characterization of exposure was good. Study details and [HYPERLINK "https://hawcprd.epa.gov/rob/study/100000968/"] can be found in HAWC.
Confidence in database	M	Confidence in the oral toxicity database for derivation of the candidate subchronic RfD for thyroid effects is medium because although there are multiple developmental toxicity studies in mice and rats, no studies are available that have specifically evaluated neurodevelopmental, immunological, or mammary gland effects. In addition, available toxicokinetic studies are limited (e.g., one mouse toxicokinetic study) and toxicokinetic data do not exist for PFBS at all life stages, including neonates, infants, and children. Additionally, studies are not available to estimate the relative cross-species sensitivity in toxicodynamics (e.g., thyroid signaling).
Confidence in candidate subchronic RfD	M	The overall confidence in the candidate subchronic RfD for thyroid effects is medium.

H = high; HAWC = Health Assessment Workspace Collaborative; K^+PFBS = potassium perfluorobutane sulfonate; M = medium; PFBS = perfluorobutane sulfonic acid; RfD = oral reference dose.

The subchronic RfD is derived to be protective of all types of effects across studies and species following oral subchronic exposure and is intended to protect sensitive subpopulations and life stages.

6.1.2 Derivation of the Chronic Oral Reference Dose

There are no chronic studies available for PFBS and K^+PFBS. Therefore, based on the same database and similar considerations as the subchronic RfD, the noncancer chronic RfD is derived, based on the same $BMDL_{0.5SD}$ (HED) of 0.095 mg/kg-day for decreased serum total T_4 in newborn (PND 1) mice [ADDIN EN.CITE <EndNote><Cite><Author>Feng</Author><Year>2017</Year><RecNum>1031</RecNum><I

DText>3856465</IDText><DisplayText>(Feng et al., 2017)</DisplayText><record><rec-number>1031</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1031</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Feng, X.</author><author>Cao, X.</author><author>Zhao, S.</author><author>Wang, X.</author><author>Hua, X.</author><author>Chen, L.</author><author>Chen, L.</author></authors></contributors><titles><title>Exposure of pregnant mice to perfluorobutanesulfonate causes hypothyroxinemia and developmental abnormalities in female offspring</title><secondary-title>Toxicological Sciences</secondary-title><alt-title>Toxicol Sci</alt-title><short-title>Toxicological Sciences</short-title></titles><periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></periodical><alt-periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></alt-periodical><pages>409-419</pages><volume>155</volume><number>2</number><dates><year>2017</year></dates><isbn>ISSN 1096-6080
EISSN 1096-0929</isbn><accession-num>27803384</accession-num><label>3856465</label><urls><related-urls><url>http://dx.doi.org/10.1093/toxsci/kfw219</url></related-urls></urls><electronic-resource-num>10.1093/toxsci/kfw219</electronic-resource-num><language>English</language></record></Cite></EndNote>], as follows:

Chronic RfD for K^+PFBS $= BMDL_{0.5SD}$ (HED) ÷ UF_C
= 0.095 mg/kg-day ÷ 300
= 0.00032 mg/kg-day
= **3×10^{-4} mg/kg-day**

[REF _Ref55817975 \h] summarizes the uncertainty factors for the chronic RfD for K^+PFBS based on effects in the thyroid.

Table [SEQ Table * ARABIC]. Uncertainty Factors for the Chronic RfD for Thyroid for K^+PFBS (CASRN 29420-49-3)		
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 mice and humans following oral K^+PFBS/PFBS exposure. Some aspects of the cross-species extrapolation of toxicokinetic and toxicodynamic processes have been accounted for by calculating an HED by applying a DAF as outlined in the U.S. EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2011</Year><RecNum>1311</RecNum><IDText>752972</IDText><DisplayText>(U.S. EPA, 2011b)</DisplayText><record><rec-number>1311</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1311</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Recommended use of body weight 3/4 as the default method in derivation of the oral reference dose</title></titles><pages>1-50</pages><dates><year>2011</year></dates><pub-location>Washington, DC</pub-location><publisher>U.S. Environmental Protection Agency, Risk Assessment Forum, Office of the Science Advisor</publisher><isbn>EPA/100/R-11/0001</isbn><label>752972</label><urls><related-urls><url>https://www.epa.gov/sites/production/files/2013-09/documents/recommended-use-of-bw34.pdf</url></related-urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>]. However, some residual uncertainty remains in the relative cross-species sensitivity in toxicodynamics (e.g., thyroid signaling). Thus, in the absence of chemical-specific data to quantify these uncertainties, U.S. EPA's guidance recommends using a UF_A of 3.

Table [SEQ Table * ARABIC]. Uncertainty Factors for the Chronic RfD for Thyroid for K^+PFBS (CASRN 29420-49-3)		
UF	**Value**	**Justification**
UF_D	10	A UF_D of 10 is applied to account for database deficiencies. The oral exposure database contains multiple short-term and subchronic-duration toxicity studies of laboratory animals [ADDIN EN.CITE ADDIN EN.CITE.DATA], a two-generation reproductive toxicity study in rats [ADDIN EN.CITE <EndNote><Cite><Author>Lieder</Author><Year>2009</Year><RecNum>1044</RecNum><IDText>1578545</IDText><DisplayText>(Lieder et al., 2009b)</DisplayText><record><rec-number>1044</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1044</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lieder, P. H.</author><author>York, R. G.</author><author>Hakes, D. C.</author><author>Chang, S. C.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>A two-generation oral gavage reproduction study with potassium perfluorobutanesulfonate (K+PFBS) in Sprague Dawley rats</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>33-45</pages><volume>259</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-3185</isbn><accession-num>19428941</accession-num><label>1578545</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2009.01.027</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2009.01.027</electronic-resource-num><language>English</language></record></Cite></EndNote>], and multiple developmental toxicity studies in mice and rats [ADDIN EN.CITE ADDIN EN.CITE.DATA]. However, because thyroid hormone is known to be critical during developmental life stages, particularly for neurodevelopment, the database is limited by the lack of developmental neurotoxicity studies. Further, because of the lack of chronic studies, there is additional uncertainty regarding how longer-term exposures might affect hazard identification and dose-response assessment for PFBS via the oral route (e.g., potentially more sensitive effects). Lastly, because immunotoxicity and mammary gland development are effects of increasing concern across several members of the larger PFAS family [ADDIN EN.CITE ADDIN EN.CITE.DATA], the lack of studies evaluating these outcomes following PFBS exposure is a limitation in the database.
UF_H	10	A UF_H of 10 is applied to account for interindividual variability in the human populations because of both intrinsic (toxicokinetic, toxicodynamic, genetic, life stage, and health status) and extrinsic (lifestyle) factors that can influence the response to dose. In the absence of chemical-specific data to quantify this variability in the [SEQ CHAPTER \h \r 1]toxicokinetics and toxicodynamics of K^+PFBS/PFBS in humans, U.S. EPA recommends using a UF_H of 10.
UF_L	1	A UF_L of 1 is applied for LOAEL-to-NOAEL extrapolation because the POD is a BMDL and the BMR was selected based on evidence that it represented a minimal biologically significant response level in susceptible populations such as developing offspring.

Table [SEQ Table * ARABIC]. Uncertainty Factors for the Chronic RfD for Thyroid for K^+PFBS (CASRN 29420-49-3)		
UF	**Value**	**Justification**
UF_S	1	A UF_S of 1 is applied because the POD comes from a developmental study of mice. The developmental period is recognized as a susceptible life stage in which exposure during certain time windows (e.g., gestational) is more relevant to the induction of developmental effects than lifetime exposure [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>1991</Year><RecNum>1321</RecNum><IDText>8567</IDText><DisplayText>(U.S. EPA, 1991b)</DisplayText><record><rec-number>1321</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1321</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Guidelines for developmental toxicity risk assessment</title></titles><pages>1-71</pages><dates><year>1991</year></dates><pub-location>Washington, DC</pub-location><publisher>U.S. Environmental Protection Agency, Risk Assessment Forum</publisher><isbn>EPA/600/FR-91/001</isbn><label>8567</label><urls><related-urls><url>http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=23162</url></related-urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>]. The additional concern over potential hazards following longer term (chronic) exposures is accounted for under the UF_D above.
UF_C	300	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$

BMDL = benchmark dose lower confidence limit; BMR = benchmark response; DAF = dosimetric adjustment factor; HED = human equivalent dose; K^+PFBS = potassium perfluorobutane sulfonate; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; PFAS = per- and polyfluoroalkyl substances; PFBS = perfluorobutane sulfonic acid; POD = point of departure; RfD = oral 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 = subchronic-to-chronic uncertainty factor.

The data for K^+PFBS can be used to derive a chronic RfD for the free acid (PFBS), because K^+PFBS is fully dissociated in water at the environmental pH range of 4–9 [ADDIN EN.CITE <EndNote><Cite><Author>NICNAS</Author><Year>2005</Year><RecNum>1306</RecNum><IDText>1784741</IDText><DisplayText>(NICNAS, 2005)</DisplayText><record><rec-number>1306</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1306</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NICNAS,</author></authors></contributors><titles><title>Existing chemical hazard assessment report. Potassium perfluorbutane sulfonate</title></titles><dates><year>2005</year></dates><pub-location>Canberra, Australia</pub-location><publisher>Commonwealth of Australia, Australian Government Publishing</publisher><label>1784741</label><urls><related-urls><url>https://web.archive.org/web/20200503121653/http://www.nicnas.gov.au/__data/assets/pdf_file/0004/4927/Potassium_Perfluorobutane_Sulfonate_PDF.pdf</url></related-urls></urls><language>English</language><modified-date>National Industrial Chemicals Notification and Assessment Scheme</modified-date></record></Cite></EndNote>]. To

calculate the chronic RfD for the free acid, the chronic RfD for the potassium salt is adjusted to compensate for differences in MW between K^+PFBS (338.19) and PFBS (300.10). The chronic RfD for PFBS (free acid) for thyroid effects is the same as the value for the K^+PFBS salt. The chronic RfD for PFBS (free acid) is calculated as follows:

Chronic RfD	=	RfD for K^+PFBS salt × (MW free acid ÷ MW salt)
for PFBS (free acid)	=	0.00032 mg/kg-day × (300.10 ÷ 338.19)
	=	0.00032 mg/kg-day × (0.89)
	=	0.00028 mg/kg-day
	=	**3×10^{-4} mg/kg-day**

Confidence in the chronic RfD for PFBS and K^+PFBS for thyroid effects is low, as explained in Table 13 below.

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Table [SEQ Table * ARABIC]. Confidence Descriptors for Chronic RfD for PFBS (CASRN 375-73-5) and the Related Compound K^+PFBS (CASRN 29420-49-3)

Confidence Categories	Designation	Discussion
Confidence in study	H	Confidence in the principal study is high because the overall study design, performance, and characterization of exposure was good. Study details and [HYPERLINK "https://hawcprd.epa.gov/rob/study/100000968/"] can be found in HAWC.
Confidence in database	L	Confidence in the oral toxicity database for deriving the chronic RfD is low because, although there are multiple short-term studies and a subchronic-duration toxicity study in laboratory animals, one acceptable two-generation reproductive toxicity study in rats, and multiple developmental toxicity studies in mice and rats, the database lacks any chronic-duration exposure studies or studies that have evaluated neurodevelopmental, immunological, or mammary gland effects. In addition, available toxicokinetic studies are limited (e.g., one mouse toxicokinetic study) and toxicokinetic data do not exist for PFBS at all life stages, including neonates, infants, and children. Additionally, studies are not available to estimate the relative cross-species sensitivity in toxicodynamics (e.g., thyroid signaling).
Confidence in candidate chronic RfD	L	The overall confidence in the candidate chronic RfD for thyroid effects is low.

H = high; HAWC = Health Assessment Workspace Collaborative; K^+PFBS = potassium perfluorobutane sulfonate; L = low; PFBS = perfluorobutane sulfonic acid; RfD = oral reference dose.

The chronic RfD is derived to be protective of all types of effects across studies and species following oral chronic exposure and is intended to protect the population as a whole, including potentially susceptible populations and life stages [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2002</Year><RecNum>1316</RecNum><IDText>88824</IDText><DisplayText>(U.S. EPA, 2002)</DisplayText><record><rec-number>1316</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1316</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>A review of the reference dose and reference concentration processes</title></titles><dates><year>2002</year></dates><pub-location>Washington, DC</pub-location><publisher>U.S. Environmental Protection Agency, Risk Assessment Forum</publisher><isbn>EPA/630/P-02/002F</isbn><label>88824</label><urls><related-urls><url>https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf</url></related-urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>]. This value should be applied in general population risk assessments. Decisions concerning averaging exposures over time for comparison with the RfD should consider the types of toxicological effects and specific life stages of concern. For example, fluctuations in exposure levels that

result in elevated exposures during development could potentially lead to an appreciable risk, even if average levels over the full exposure duration were less than or equal to the RfD.

6.2 DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

No published studies investigating the effects of subchronic- or chronic-duration inhalation toxicity of PFBS and the related compound K^+PFBS in humans or animals have been identified.

6.3 CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR AND DERIVATION OF CANCER RISK VALUES

No studies evaluating the carcinogenicity of PFBS or K^+PFBS in humans or animals have been identified. In accordance with the *Guidelines for Carcinogen Risk Assessment* [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2005</Year><RecNum>1222</RecNum><IDText>6324329</IDText><DisplayText>(U.S. EPA, 2005)</DisplayText><record><rec-number>1222</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1222</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Guidelines for carcinogen risk assessment</title></titles><dates><year>2005</year></dates><pub-location>Washington, DC</pub-location><publisher>U.S. Environmental Protection Agency, Risk Assessment Forum</publisher><isbn>EPA/630/P-03/001B</isbn><label>6324329</label><work-type>EPA Report</work-type><urls><related-urls><url>https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf</url></related-urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>], the U.S. EPA concluded that there is *"Inadequate Information to Assess Carcinogenic Potential"* for PFBS and K^+PFBS by any route of exposure. Therefore, the lack of data on the carcinogenicity of PFBS and the related compound K^+PFBS precludes the derivation of quantitative estimates for either oral (oral slope factor) or inhalation (inhalation unit risk) exposure.

6.4 SUSCEPTIBLE POPULATIONS AND LIFE STAGES

Early life stages as well as pregnant women are potentially susceptible to PFBS exposure. PFBS has been detected in blood serum of nursing mothers, which might indicate a potential for lactational exposure [ADDIN EN.CITE <EndNote><Cite><Author>Glynn</Author><Year>2012</Year><RecNum>924</RecNum><IDText>1578498</IDText><DisplayText>(Glynn et al., 2012)</DisplayText><record><rec-number>924</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">924</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Glynn, A.</author><author>Berger, U.</author><author>Bignert, A.</author><author>Ullah, S.</author><author>Aune, M.</author><author>Lignell, S.</author><author>Darnerud, P. O.</author></authors></contributors><titles><title>Perfluorinated alkyl acids in blood serum from primiparous women in Sweden: serial sampling during pregnancy and nursing, and temporal trends 1996-2010</title><secondary-title>Environmental Science and Technology</secondary-title><alt-title>Environ Sci Technol</alt-title><short-

title>Environmental Science and Technology</short-title></titles><periodical><full-title>Environmental Science and Technology</full-title><abbr-1>Environ Sci Technol</abbr-1></periodical><alt-periodical><full-title>Environmental Science and Technology</full-title><abbr-1>Environ Sci Technol</abbr-1></alt-periodical><pages>9071-9079</pages><volume>46</volume><number>16</number><dates><year>2012</year></dates><isbn>ISSN 0013-936X
EISSN 1520-5851</isbn><accession-num>22770559</accession-num><label>1578498</label><urls><related-urls><url>http://dx.doi.org/10.1021/es301168c</url></related-urls></urls><electronic-resource-num>10.1021/es301168c</electronic-resource-num><language>English</language></record></Cite></EndNote>]; however, information on the kinetics of lactational transfer are lacking and represents a key data gap for future research.

The available information suggests sex-specific variation in the toxicokinetics of PFBS in rodents. Studies in mice and rats generally report clearance and elimination half-lives to be faster for females than for males (see the "Toxicokinetics" section). For example, [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6579272"] reports statistically significant differences in half-life between the sexes with female mice exhibiting a shorter half-life than males. Similar sex-specific variation in elimination has been reported in rats. [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1326734"] reported a statistically significant difference in the urinary clearance rates ($p \leq 0.01$), with female rats (469 ± 40 mL/hour) having faster clearance rates than male rats (119 ± 34 mL/hour). [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5387170"] also reported higher clearance in female rats than in male rats given the same dose (26.0−75.5 mL/hour-kg in males, 152−259 mL/hour-kg in females). [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=2850396"] reported that the mean apparent clearance of PFBS from the serum was approximately eightfold higher for female rats (0.311 L/hour-kg) than for male rats (0.0394 L/hour-kg). Statistically significant sex-related differences in half-life or clearance were not observed between male and female monkeys [ADDIN EN.CITE <EndNote><Cite><Author>Olsen</Author><Year>2009</Year><RecNum>1045</RecNum><IDText>1326734</IDText><DisplayText>(Olsen et al., 2009)</DisplayText><record><rec-number>1045</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1045</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Olsen, G. W.</author><author>Chang, S. C.</author><author>Noker, P. E.</author><author>Gorman, G. S.</author><author>Ehresman, D. J.</author><author>Lieder, P. H.</author><author>Butenhoff, J. L.</author></authors></contributors><titles><title>A comparison of the pharmacokinetics of perfluorobutanesulfonate (PFBS) in rats, monkeys, and humans</title><secondary-title>Toxicology</secondary-title><alt-title>Toxicology</alt-title><short-title>Toxicology</short-title></titles><periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></periodical><alt-periodical><full-title>Toxicology</full-title><abbr-1>Toxicology</abbr-1></alt-periodical><pages>65-74</pages><volume>256</volume><number>1-2</number><dates><year>2009</year></dates><isbn>ISSN 0300-483X
EISSN 1879-

3185</isbn><accession-num>19059455</accession-num><label>1326734</label><urls><related-urls><url>http://dx.doi.org/10.1016/j.tox.2008.11.008</url></related-urls></urls><electronic-resource-num>10.1016/j.tox.2008.11.008</electronic-resource-num><language>English</language></record></Cite></EndNote>]. Differences in the toxicokinetics in rodents could result in sex-specific differences in toxicity studies.

In vivo toxicity studies report that PFBS exposure can alter thyroid hormone levels in parental and F_1 generation animals (see the "Thyroid Effects" section). Thyroid hormones play a critical role in coordinating complex developmental processes for various organs/systems (e.g., reproductive and nervous system), and disruption of thyroid hormone production/levels in a pregnant woman or neonate can have persistent adverse health effects for the developing offspring [ADDIN EN.CITE ADDIN EN.CITE.DATA].

Animal studies also provide evidence that gestationally exposed females might be a susceptible subpopulation because of potential effects on female reproduction, including evidence of altered ovarian follicle development and delayed vaginal opening (see the "Reproductive Effects" section). Furthermore, gestationally exposed females also had significantly reduced BWs and delayed eye opening. These findings suggest that developmental landmarks indicative of adverse responses can be affected after PFBS exposure (see the "Offspring Growth and Early Development" section).

APPENDIX A. LITERATURE SEARCH STRATEGY

This appendix presents the full details of the literature search strategy used to identify primary, peer-reviewed literature pertaining to perfluorobutane sulfonic acid (PFBS) (Chemical Abstracts Service registry number [CASRN] 375-73-5) and/or the potassium salt (K^+PFBS) (CASRN 29420-49-3) and the deprotonated anionic form of PFBS (i.e., $PFBS^-$; CASRN 45187-15-3). Initial database searches were conducted on July 18, 2017 using four online scientific databases (PubMed, Web of Science [WOS], TOXLINE, and TSCATS via TOXLINE) and updated on February 28, 2018; May 1, 2019; and May 15, 2020. The literature search focused on chemical name and synonyms (see [REF _Ref55818606 \h]) with no limitations on publication type, evidence stream (i.e., human, animal, in vitro, and in silico) or health outcomes. Beyond database searches, references were also identified from studies submitted under the Toxic Substances Control Act (TSCA) and from review of other government documents (e.g., Agency for Toxic Substances and Disease Registry [ATSDR]) and combined with the results of the database search. Search results are retained in the U.S. EPA's Health and Environmental Research Online (HERO) database.

Table A-[SEQ Table_A- * ARABIC]. Synonyms and MeSH Terms

ChemID	375-73-5 1,1,2,2,3,3,4,4,4-Nonafluoro-1-butanesulfonic acid 1-Perfluorobutanesulfonic acid Nonafluoro-1-butanesulfonic acid Nonafluorobutanesulfonic acid Perfluorobutanesulfonic acid PFBS 1,1,2,2,3,3,4,4,4-Nonafluorobutane-1-sulphonic acid
PubMed (new only)	Perfluorobutane sulfonic acid Perfluorobutanesulfonate Perfluorobutane sulfonate
EPA Spreadsheet	1,1,2,2,3,3,4,4,4-Nonafluoro-1-butanesulfonic acid 1-Butanesulfonic acid, 1,1,2,2,3,3,4,4,4-nonafluoro- 1-Butanesulfonic acid, nonafluoro- 1-Perfluorobutanesulfonic acid Nonafluoro-1-butanesulfonic acid Nonafluorobutanesulfonic acid PFBS Perfluoro-1-butanesulfonate Perfluorobutane sulfonate Perfluorobutanesulfonate Perfluorobutanesulfonic acid Perfluorobutylsulfonate 45187-15-3

MeSH = medical subject headings; PFBS = perfluorobutane sulfonic acid.

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A.1. LITERATURE SEARCH STRINGS

PubMed

375-73-5[rn] OR 45187-15-3[rn] "nonafluorobutane-1-sulfonic acid"[nm] OR "1,1,2,2,3,3,4,4,4-Nonafluoro-1-butanesulfonic acid"[tw] OR "1-Perfluorobutanesulfonic acid"[tw] OR "Nonafluoro-1-butanesulfonic acid"[tw] OR "Nonafluorobutanesulfonic acid"[tw] OR "Perfluorobutanesulfonic acid"[tw] OR "1,1,2,2,3,3,4,4,4-Nonafluorobutane-1-sulphonic acid"[tw] OR "Perfluorobutane sulfonic acid"[tw] OR "Perfluorobutanesulfonate"[tw] OR "Perfluorobutane sulfonate"[tw] OR "1-Butanesulfonic acid, 1,1,2,2,3,3,4,4,4-nonafluoro-"[tw] OR "1-Butanesulfonic acid, nonafluoro-"[tw] OR "Perfluoro-1-butanesulfonate"[tw] OR "Perfluorobutylsulfonate"[tw] OR "Eftop FBSA"[tw] OR (PFBS[tw] AND (fluorocarbon*[tw] OR fluorotelomer*[tw] OR polyfluoro*[tw] OR perfluoro-*[tw] OR perfluoroa*[tw] OR perfluorob*[tw] OR perfluoroc*[tw] OR perfluorod*[tw] OR perfluoroe*[tw] OR perfluoroh*[tw] OR perfluoron*[tw] OR perfluoroo*[tw] OR perfluorop*[tw] OR perfluoros*[tw] OR perfluorou*[tw] OR perfluorinated[tw] OR fluorinated[tw] OR PFAS[tw] OR PFOS[tw] OR PFOA[tw]))

WOS

TS="1,1,2,2,3,3,4,4,4-Nonafluoro-1-butanesulfonic acid" OR TS="1-Perfluorobutanesulfonic acid" OR TS="Nonafluoro-1-butanesulfonic acid" OR TS="Nonafluorobutanesulfonic acid" OR TS="Perfluorobutanesulfonic acid" OR TS="1,1,2,2,3,3,4,4,4-Nonafluorobutane-1-sulphonic acid" OR TS="Perfluorobutane sulfonic acid" OR TS="Perfluorobutanesulfonate" OR TS="Perfluorobutane sulfonate" OR TS="1-Butanesulfonic acid, 1,1,2,2,3,3,4,4,4-nonafluoro-" OR TS="1-Butanesulfonic acid, nonafluoro-" OR TS="Perfluoro-1-butanesulfonate" OR TS="Perfluorobutylsulfonate" OR TS="Eftop FBSA" OR (TS=PFBS AND TS=(fluorocarbon* OR fluorotelomer* OR polyfluoro* OR perfluoro-* OR perfluoroa* OR perfluorob* OR perfluoroc* OR perfluorod* OR perfluoroe* OR perfluoroh* OR perfluoron* OR perfluoroo* OR perfluorop* OR perfluoros* OR perfluorou* OR perfluorinated OR fluorinated OR PFAS OR PFOS OR PFOA))

TOXLINE

((375-73-5 [rn] OR 45187-15-3 [rn] OR "1 1 2 2 3 3 4 4 4-nonafluoro-1-butanesulfonic acid" OR "1-perfluorobutanesulfonic acid" OR "nonafluoro-1-butanesulfonic acid" OR "nonafluorobutanesulfonic acid" OR "perfluorobutanesulfonic acid" OR "1 1 2 2 3 3 4 4 4-nonafluorobutane-1-sulphonic acid" OR "perfluorobutane sulfonic acid" OR "perfluorobutanesulfonate" OR "perfluorobutane sulfonate" OR "1-butanesulfonic acid 1 1 2 2 3 3 4 4 4-nonafluoro-" OR "1-butanesulfonic acid nonafluoro-" OR "perfluoro-1-butanesulfonate" OR "perfluorobutylsulfonate" OR "eftop fbsa" OR (pfbs AND (fluorocarbon* OR fluorotelomer* OR polyfluoro* OR perfluoro* OR perfluorinated OR fluorinated OR pfas OR pfos OR pfoa)))) AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]

TSCATS

375-73-5[rn] AND tscats[org]; 45187-15-3[rn] AND tscats[org]

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APPENDIX B. DETAILED PECO CRITERIA

Table B-[SEQ Table_B- * ARABIC]. Population, Exposure, Comparator, and Outcome Criteria

PECO Element	Evidence
Population	**Human:** Any population (occupational; general population including children, pregnant women, and other sensitive populations). The following study designs will be considered most informative: controlled exposure, cohort, case-control, or cross-sectional. Note: Case reports and case series are not the primary focus of this assessment and will be tracked as supplemental material during the study screening process. **Animal:** Nonhuman mammalian animal species (whole organism) of any life stage (including preconception, in utero, lactation, peripubertal, and adult stages). **In vitro models of genotoxicity:** The studies will be considered PECO relevant. All other in vitro studies will be tagged as "non-PECO relevant, but supplemental material." **Nonmammalian model systems/in vitro/in silico NOT related to genotoxicity:** Nonmammalian model systems (e.g., fish, amphibians, birds, and *Caenorhabditis elegans*); studies of human or animal cells, tissues, or biochemical reactions (e.g., ligand binding assays) with in vitro exposure regimens; bioinformatics pathways of disease analysis; and/or high throughput screening data. These studies will be classified as non-PECO relevant, but have supplemental information.
Exposure	**Human:** Studies providing qualitative or quantitative estimates of exposure based on administered dose or concentration, biomonitoring data (e.g., urine, blood, or other specimens), environmental or occupational-setting measures (e.g., water levels or air concentrations), residential location, job title or other relevant occupational information. Human "mixture" studies are considered PECO relevant as long as they have the PFAS of interest. **Animal:** Studies providing qualitative and quantitative estimates of exposure based on administered dose or concentration. Oral and inhalation studies are considered PECO relevant. Nonoral and noninhalation studies are tagged as supplemental. Experimental mixture studies are included as PECO relevant only if they include a PFBS-only arm. Otherwise, mixture studies are tagged as supplemental. All studies must include exposure to PFBS, CASRN 375-73-5. Studies of precursor PFAS that identify any of the targeted PFAS as metabolites will also be included.
Comparator	**Human:** A comparison or reference population exposed to lower levels (or no exposure/exposure below detection levels) or for shorter periods of time. For D-R purposes, exposure-response quantitative results must be presented in sufficient detail such as regression coefficients presented with statistical measure of variation such as RR, HR, OR, or SMR or observed cases vs. expected cases (common in occupational studies); slope or linear regression coefficient (i.e., per unit increase in a continuous outcome); difference in the means; or report means with results of *t*-test, mean comparison by regression, or other mean-comparing hypothesis test. **Animal:** Quantitative exposure versus lower or no exposure with concurrent vehicle control group.
Outcome	Cancer and noncancer health outcomes. In general, endpoints related to clinical diagnostic criteria, disease outcomes, histopathological examination, genotoxicity, or other apical/phenotypic outcomes will be prioritized for evidence synthesis. Based on preliminary screening work and other assessments, the systematic review is anticipated to focus on liver (including serum lipids), developmental, reproductive, neurological, developmental neurotoxicity, thyroid disease/disruption, immunological, cardiovascular, and musculoskeletal outcomes.

D-R = dose-response; HR = hazard ratio; OR = odds ratio; PECO = Population, Exposure, Comparator, and Outcome; PFAS = per- and polyfluoroalkyl substances; PFBS = perfluorobutane sulfonic acid; RR = risk ratio; SMR = standardized mortality ratio

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APPENDIX C. STUDY EVALUATION METHODS

For each outcome in a study, in each domain, reviewers reached a consensus judgment of *good, adequate, deficient, not reported,* or *critically deficient*. Questions used to guide the development of criteria for each domain in epidemiology studies are presented in [REF _Ref55818646 \h] and experimental animal toxicology studies in [REF _Ref55818670 \h]. These categories were applied to each evaluation domain for each study as follows:

- *Good* represents a judgment that the study was conducted appropriately in relation to the evaluation domain and any deficiencies, if present, are minor and would not be expected to influence the study results.
- *Adequate* indicates a judgment that there are methodological limitations relating to the evaluation domain, but that those limitations are not likely to be severe or to have a notable impact on the results.
- *Deficient* denotes identified biases or deficiencies that are interpreted as likely to have had a notable impact on the results or that prevent interpretation of the study findings.
- *Not reported* indicates that the information necessary to evaluate the domain was not available in the study. Generally, this term carries the same functional interpretation as *deficient* for the purposes of the study confidence classification. Depending on the number and severity of other limitations identified in the study, it may or may not be worth reaching out to the study authors for this information.
- *Critically deficient* reflects a judgment that the study conduct introduced a serious flaw that makes the observed effect(s) uninterpretable. Studies with a determination of critically deficient in an evaluation domain will almost always cause the study to be considered overall *uninformative*.

Once the evaluation domains were rated, the identified strengths and limitations were considered to reach a study confidence rating of *high, medium, low*, or *uninformative* for a specific health outcome. This was based on the reviewer judgments across the evaluation domains and included consideration of the likely impact the noted deficiencies in bias and sensitivity, or inadequate reporting, have on the results. The ratings, which reflect a consensus judgment between reviewers, are defined as follows:

- *High*: A well-conducted study with no notable deficiencies or concerns were identified; 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 satisfactory (acceptable) study in which deficiencies or concerns were noted, 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 substandard study in which deficiencies or concerns were noted, 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 could have a *deficient* rating in domain(s) considered to have less influence on the magnitude or

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direction of effect estimates. Generally, *low* confidence results are given less weight than *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 bias towards the null require additional consideration during evidence synthesis. Observing an effect in these studies could increase confidence, assuming the study was otherwise well-conducted.

- *Uninformative*: An unacceptable study in which serious flaw(s) make the study results unusable for informing hazard identification. 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 might also be considered *uninformative*. *Uninformative* studies will not be considered further in the synthesis and integration of evidence for hazard identification or dose-response but might be used to highlight possible research gaps.

Table C-[SEQ Table_C- * ARABIC]. Questions Used to Guide the Development of Criteria for Each Domain in Epidemiology Studies

Core Question	Prompting Questions	Follow-Up Questions
Exposure measurement Does the exposure measure reliably distinguish between levels of exposure in a time window considered most relevant for a causal effect with respect to the development of the outcome?	For all: • Does the exposure measure capture the variability in exposure among the participants, considering intensity, frequency, and duration of exposure? • Does the exposure measure reflect a relevant time window? If not, can the relationship between measures in this time and the relevant time window be estimated reliably? • Was the exposure measurement likely to be affected by a knowledge of the outcome? • Was the exposure measurement likely to be affected by the presence of the outcome (i.e., reverse causality)? For case-control studies of occupational exposures: • Is exposure based on a comprehensive job history describing tasks, setting, time period, and use of specific materials? For biomarkers of exposure, general population: • Is a standard assay used? What are the intra- and interassay coefficients of variation? Is the assay likely to be affected by contamination? Are values less than the limit of detection dealt with adequately? What exposure time period is reflected by the biomarker? If the half-life is short, what is the correlation between serial measurements of exposure?	Is the degree of exposure misclassification likely to vary by exposure level? If the correlation between exposure measurements is moderate, is there an adequate statistical approach to ameliorate variability in measurements? If there is a concern about the potential for bias, what is the predicted direction or distortion of the bias on the effect estimate (if there is enough information)?

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Table C-[SEQ Table_C- * ARABIC]. Questions Used to Guide the Development of Criteria for Each Domain in Epidemiology Studies

Core Question	Prompting Questions	Follow-Up Questions
Outcome ascertainment Does the outcome measure reliably distinguish the presence or absence (or degree of severity) of the outcome?	For all: • Is outcome ascertainment likely to be affected by knowledge of, or presence of, exposure (e.g., consider access to health care, if based on self-reported history of diagnosis)? For case-control studies: • Is the comparison group without the outcome (e.g., controls in a case-control study) based on objective criteria with little or no likelihood of inclusion of people with the disease? For mortality measures: • How well does cause of death data reflect occurrence of the disease in an individual? How well do mortality data reflect incidence of the disease? For diagnosis of disease measures: • Is diagnosis based on standard clinical criteria? If based on self-report of diagnosis, what is the validity of this measure? For laboratory-based measures (e.g., hormone levels): • Is a standard assay used? Does the assay have an acceptable level of interassay variability? Is the sensitivity of the assay appropriate for the outcome measure in this study population?	Is there a concern that any outcome misclassification is nondifferential, differential, or both? What is the predicted direction or distortion of the bias on the effect estimate (if there is enough information)?
Participant selection Is there evidence that selection into or out of the study (or analysis sample) was jointly related to exposure and to outcome?	For longitudinal cohort: • Did participants volunteer for the cohort based on knowledge of exposure and/or preclinical disease symptoms? Was entry into the cohort or continuation in the cohort related to exposure and outcome? For occupational cohort: • Did entry into the cohort begin with the start of the exposure? • Was follow-up or outcome assessment incomplete, and if so, was follow-up related to both exposure and outcome status? • Could exposure produce symptoms that would result in a change in work assignment/work status ("healthy worker survivor effect")? For case-control study: • Were controls representative of population and time periods from which cases were drawn? • Are hospital controls selected from a group whose reason for admission is independent of exposure? • Could recruitment strategies, eligibility criteria, or participation rates result in differential participation relating to both disease and exposure? For population-based survey: • Was recruitment based on advertisement to people with knowledge of exposure, outcome, and hypothesis?	Were differences in participant enrollment and follow-up evaluated to assess bias? If there is a concern about the potential for bias, what is the predicted direction or distortion of the bias on the effect estimate (if there is enough information)? Were appropriate analyses performed to address changing exposures over time in relation to symptoms? Is there a comparison of participants and nonparticipants to address whether differential selection is likely?

Table C-[SEQ Table_C- * ARABIC]. Questions Used to Guide the Development of Criteria for Each Domain in Epidemiology Studies

Core Question	Prompting Questions	Follow-Up Questions
Confounding Is confounding of the effect of the exposure likely?	Is confounding adequately addressed by considerations in… a. …participant selection (matching or restriction)? b. …accurate information on potential confounders and statistical adjustment procedures? c. …lack of association between confounder and outcome or confounder and exposure in the study? d. …information from other sources? Is the assessment of confounders based on a thoughtful review of published literature, potential relationships (e.g., as can be gained through directed acyclic graphing), minimizing potential overcontrol (e.g., inclusion of a variable on the pathway between exposure and outcome)?	If there is a concern about the potential for bias, what is the predicted direction or distortion of the bias on the effect estimate (if there is enough information)?
Analysis Do the analysis strategy and presentation convey the necessary familiarity with the data and assumptions?	• Are missing outcome, exposure, and covariate data recognized and, if necessary, accounted for in the analysis? • Does the analysis appropriately consider variable distributions and modeling assumptions? • Does the analysis appropriately consider subgroups of interest (e.g., based on variability in exposure level, duration, or susceptibility)? • Is an appropriate analysis used for the study design? • Is effect modification considered, based on considerations developed a priori? • Does the study include additional analyses addressing potential biases or limitations (i.e., sensitivity analyses)?	If there is a concern about the potential for bias, what is the predicted direction or distortion of the bias on the effect estimate (if there is enough information)?
Sensitivity Is there a concern that sensitivity of the study is not adequate to detect an effect?	• Is the exposure range adequate? • Was the appropriate population included? • Was the length of follow-up adequate? Is the time/age of outcome ascertainment optimal given the interval of exposure and the health outcome? • Are there other aspects related to risk of bias or otherwise that raise concerns about sensitivity?	
Selective reporting Is there reason to be concerned about selective reporting?	• Are the results needed for the IRIS analysis presented (based on a priori specification)? If not, can these results be obtained? • Are only statistically significant results presented?	

IRIS = Integrated Risk Information System.

C.1. EXPOSURE MEASUREMENT EVALUATION CRITERIA

The criteria used to evaluate exposure measurement for PFBS ([REF _Ref55818660 \h]) are adapted from the criteria developed by the National Toxicology Program (NTP) Office of Health Assessment and Translation for their assessment of the association between perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) and immune effects [ADDIN EN.CITE <EndNote><Cite><Author>NTP</Author><Year>2016</Year><RecNum>1236</RecNum><IDText>4613766</IDText><DisplayText>(NTP, 2016, 2015)</DisplayText><record><rec-number>1236</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1236</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NTP,</author></authors></contributors><titles><title>NTP Monograph: Immunotoxicity associated with exposure to perfluorooctanoic acid (PFOA) or perfluorooctane sulfonate (PFOS)</title></titles><dates><year>2016</year></dates><pub-location>Research Triangle Park, NC</pub-location><publisher>U.S. Department of Health and Human Services, Office of Health Assessment and Translation</publisher><label>4613766</label><work-type>NTP</work-type><urls><related-urls><url>https://ntp.niehs.nih.gov/ntp/ohat/pfoa_pfos/pfoa_pfosmonograph_508.pdf</url></related-urls></urls><language>English</language><modified-date>National Toxicology Program</modified-date></record></Cite><Cite><Author>NTP</Author><Year>2015</Year><RecNum>574</RecNum><IDText>4613767</IDText><record><rec-number>574</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604955588">574</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>NTP,</author></authors></contributors><titles><title>Protocol to evaluate the evidence for an association between perfluorooctanoic acid (PFOA) or perfluorooctane sulfonate (PFOS) exposure and immunotoxicity</title></titles><dates><year>2015</year></dates><publisher>Department of Health and Human Services, Office of Health Assessment and Translation</publisher><label>4613767</label><urls><related-urls><url>https://ntp.niehs.nih.gov/ntp/ohat/pfoa_pfos/protocol_201506_508.pdf</url></related-urls></urls><language>English</language><modified-date>National Toxicology Program</modified-date></record></Cite></EndNote>] and were established prior to beginning study evaluation. Standard analytical methods for evaluating individual per- and polyfluoroalkyl substances (PFAS) in serum or whole-blood using quantitative techniques such as liquid chromatography-triple quadrupole mass spectrometry are preferred [ADDIN EN.CITE ADDIN EN.CITE.DATA]. The estimated serum half-life of PFBS is approximately 1 month [ADDIN EN.CITE ADDIN EN.CITE.DATA], so unlike for some other PFAS with longer half-lives, current exposure might not be indicative of past exposures. Little data is available on repeated measures of PFBS in humans over time, so the reliability of a single measure is unclear. The timing of the exposure measurement is considered in relation to the etiologic window for each outcome being reviewed.

Table C-[SEQ Table_C- * ARABIC]. Criteria for Evaluation of Exposure Measurement in Epidemiology Studies	
Exposure Measurement Rating	**Criteria**
Good	All of the following: • Evidence that exposure was consistently assessed using well-established methods that directly measure exposure (e.g., measurement of PFAS in blood, serum, or plasma). • Exposure was assessed in a relevant time window for development of the outcome (i.e., temporality is established, and sufficient latency occurred prior to disease onset). • There is evidence that a sufficient proportion of the exposure data measurements are above the limit of quantification for the assay so that different exposure groups can be distinguished based on the analyses conducted. • The laboratory analysis included standard quality control measures with demonstrated precision and accuracy. • There is sufficient specificity/sensitivity and range or variation in exposure measurements that would minimize potential for exposure measurement error and misclassification by allowing exposure classifications to be differentiated (i.e., can reliably categorize participants into groups such as high vs. low exposure).
Adequate	• Evidence that exposure was consistently assessed using well-established methods that directly measure exposure (e.g., measurement of PFAS in blood, serum, or plasma), but there were some minor concerns about quality control measures or other potential for nondifferential misclassification. OR • Exposure was assessed using indirect measures (e.g., drinking water concentrations and residential location/history, questionnaire, or occupational exposure assessment by a certified industrial hygienist) that have been validated or empirically shown to be consistent with methods that directly measure exposure (i.e., intermethods validation: one method vs. another). Note: This could be *good* if the validation was sufficient. All studies for PFBS used direct measures. And all of the following: • Exposure was assessed in a relevant time window for development of the outcome. • There is evidence that a sufficient proportion of the exposure data measurements are above the limit of quantification for the assay. • There is sufficient specificity/sensitivity and range or variation in exposure measurements that would minimize potential for exposure measurement error and misclassification by allowing exposure classifications to be differentiated (i.e., can reliably categorize participants into groups such as high vs. low exposure), but there might be more uncertainty than in *good*.

Table C-[SEQ Table_C- * ARABIC]. Criteria for Evaluation of Exposure Measurement in Epidemiology Studies	
Exposure Measurement Rating	**Criteria**
Deficient	Any of the following: • Some concern, but no direct evidence, that the exposure was assessed using poorly validated methods. • There is insufficient information provided about the exposure assessment, including precision, accuracy, and level of quantification, but no evidence for concern about the method used. • Exposure was assessed in a relevant time window for development of the outcome. There could be concerns about reverse causation between exposure and outcome, but there is no direct evidence that it is present. • There is some concern over insufficient specificity/sensitivity and range or variation in exposure measurements that may result in considerable exposure measurement error and misclassification when exposure classifications are compared (i.e., data do not lend themselves to reliably categorize participants into groups such as high vs. low exposure, and/or there is considerable uncertainty in exposure values that do not allow for confidence in the examination of small per unit changes in continuous exposures).
Critically deficient	Any of the following: • Exposure was assessed in a time window that is unknown or not relevant for development of the outcome. This could be due to clear evidence of reverse causation between exposure and outcome, or other concerns such as the lack of temporal ordering of exposure and disease onset, insufficient latency, or having exposure measurements that are not reliable measures of exposure during the etiologic window. • Direct evidence that bias was likely because the exposure was assessed using methods with poor validity. • Evidence of differential exposure misclassification (e.g., differential recall of self-reported exposure). • There is evidence that an insufficient proportion of the exposure data measurements are above the limit of quantification for the assay.

PFAS = per- and polyfluoroalkyl substances; PFBS = perfluorobutane sulfonic acid.

Table C-[SEQ Table_C- * ARABIC]. Questions Used to Guide the Development of Criteria for Each Domain in Experimental Animal Toxicology Studies

Evaluation Type	Domain– Core Question	Prompting Questions	Basic Considerations
Reporting Quality	**Reporting quality–** Does the study report information for evaluating the design and conduct of the study for the endpoint(s)/outcome(s) of interest? *Notes:* *Reviewers should reach out to study authors to obtain missing information when studies are considered key for hazard evaluation and/or dose-response.* *This domain is limited to reporting. Other aspects of the exposure methods, experimental design, and endpoint evaluation methods are evaluated using the domains related to risk of bias and study sensitivity.*	Does the study report the following? • **Critical information** necessary to perform study evaluation: ○ Species, test article name, levels and duration of exposure, route (e.g., oral, inhalation), qualitative or quantitative results for at least one endpoint of interest. • **Important information** for evaluating the study methods: ○ Test animal: strain, sex, source, and general husbandry procedures. ○ Exposure methods: source, purity, method of administration. ○ Experimental design: frequency of exposure, animal age, and life stage during exposure and at endpoint/outcome evaluation. ○ Endpoint evaluation methods: assays or procedures used to measure the endpoints/outcomes of interest.	These considerations typically do not need to be refined by assessment teams, although in some instances the **important information** may be refined depending on the endpoints/outcomes of interest or the chemical under investigation. A judgment and rationale for this domain should be given for the study. Typically, these will not change regardless of the endpoints/outcomes investigated by the study. **In the rationale, reviewers should indicate whether the study adhered to GLP, OECD, or other testing guidelines.** • *Good*: All critical and **important information** is reported or inferable for the endpoints/outcomes of interest. • *Adequate*: All **critical information** is reported but some **important information** is missing. However, the missing information is not expected to significantly impact the study evaluation. • *Deficient*: All **critical information** is reported but **important information** is missing that is expected to significantly reduce the ability to evaluate the study. • *Critically deficient*: Study report is missing any pieces of **critical information**. Studies that are *critically deficient* for reporting are *uninformative* for the overall rating and considered no further for evidence synthesis and integration.

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Table C-[SEQ Table_C- * ARABIC]. Questions Used to Guide the Development of Criteria for Each Domain in Experimental Animal Toxicology Studies

Evaluation Type		Domain– Core Question	Prompting Questions	Basic Considerations
Risk of Bias	Selection and performance bias	**Allocation–** Were animals assigned to experimental groups using a method that minimizes selection bias?	For each study: • Did each animal or litter have an equal chance of being assigned to any experimental group (i.e., random allocation)? • Is the allocation method described? • Aside from randomization, were any steps taken to balance variables across experimental groups during allocation?	These considerations typically do not need to be refined by assessment teams. A judgment and rationale for this domain should be given for each cohort or experiment in the study. • *Good*: Experimental groups were randomized, and any specific randomization procedure was described or inferable (e.g., computer-generated scheme). (Note that normalization is not the same as randomization [see response for *adequate*].) • *Adequate*: Study authors report that groups were randomized but do not describe the specific procedure used (e.g., "animals were randomized"). Alternatively, the study authors used a nonrandom method to control for important modifying factors across experimental groups (e.g., body-weight normalization). • *Not reported* (interpreted as *deficient*): No indication of randomization of groups or other methods (e.g., normalization) to control for important modifying factors across experimental groups. • *Critically deficient*: Bias in the animal allocations was reported or inferable.

Table C-[SEQ Table_C- * ARABIC]. Questions Used to Guide the Development of Criteria for Each Domain in Experimental Animal Toxicology Studies

Evaluation Type		Domain– Core Question	Prompting Questions	Basic Considerations

Risk of Bias	**Selection and performance bias**	**Observational bias/blinding–**
		Did the study implement measures to reduce observational bias?
			For each endpoint/outcome or grouping of endpoints/outcomes in a study:
			• Does the study report blinding or other methods/procedures for reducing observational bias?
			• If not, did the study use a design or approach for which such procedures can be inferred?
			• What is the expected impact of failure to implement (or report implementation) of these methods/procedures on results?
				These considerations typically do not need to be refined by the assessment teams. (Note that it can be useful for teams to identify highly subjective measures of endpoints/outcomes where observational bias may strongly influence results prior to performing evaluations.)
				A judgment and rationale for this domain should be given for each endpoint/outcome or group of endpoints/outcomes investigated in the study.
				• *Good*: Measures to reduce observational bias were described (e.g., blinding to conceal treatment groups during endpoint evaluation; consensus-based evaluations of histopathology lesions).[a]
				• *Adequate*: Methods for reducing observational bias (e.g., blinding) can be inferred or were reported but described incompletely.
				• *Not reported*: Measures to reduce observational bias were not described.
				  ○ Interpreted as *adequate*—The potential concern for bias was mitigated based on use of automated/computer-driven systems; standard laboratory kits; relatively simple, objective measures (e.g., body or tissue weight); or screening-level evaluations of histopathology.
				  ○ Interpreted as *deficient*—The potential impact on the results is major (e.g., outcome measures are highly subjective).
				• *Critically deficient*: Strong evidence for observational bias that could have impacted results.

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Table C-[SEQ Table_C- * ARABIC]. Questions Used to Guide the Development of Criteria for Each Domain in Experimental Animal Toxicology Studies

Evaluation Type		Domain– Core Question	Prompting Questions	Basic Considerations
Risk of Bias	Confounding/ variable control	**Confounding–** Are variables with the potential to confound or modify results controlled for and consistent across all experimental groups?	For each study: • Are there differences across the treatment groups (e.g., co-exposures, vehicle, diet, palatability, husbandry, health status, and so forth) that could bias the results? • If differences are identified, to what extent are they expected to impact the results?	These considerations may need to be refined by assessment teams, as the specific variables of concern can vary by experiment or chemical. A judgment and rationale for this domain should be given for each cohort or experiment in the study, noting when the potential for confounding is restricted to specific endpoints/outcomes. • *Good*: Outside of the exposure of interest, variables that are likely to confound or modify results appear to be controlled for and consistent across experimental groups. • *Adequate*: Some concern that variables that were likely to confound or modify results were uncontrolled or inconsistent across groups but are expected to have a minimal impact on the results. • *Deficient*: Notable concern that potentially confounding variables were uncontrolled or inconsistent across groups and are expected to substantially impact the results. • *Critically deficient*: Confounding variables were presumed to be uncontrolled or inconsistent across groups and are expected to be a primary driver of the results.

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Table C-[SEQ Table_C- * ARABIC]. Questions Used to Guide the Development of Criteria for Each Domain in Experimental Animal Toxicology Studies

Evaluation Type		Domain– Core Question	Prompting Questions	Basic Considerations
Risk of Bias	**Reporting and attrition bias**	**Selective reporting and attrition–** Did the study report results for all prespecified outcomes and tested animals? *Note:* *This domain does **not** consider the appropriateness of the analysis/results presentation. This aspect of study quality is evaluated in another domain.*	For each study: *Selective reporting bias:* • Are all results presented for endpoints/outcomes described in the methods (see note)? *Attrition bias:* • Are all animals accounted for in the results? • If there are discrepancies, do study authors provide an explanation (e.g., death or unscheduled sacrifice during the study)? • If unexplained results, omissions, and/or attrition are identified, what is the expected impact on the interpretation of the results?	These considerations typically do not need to be refined by assessment teams. A judgment and rationale for this domain should be given for each cohort or experiment in the study. • *Good*: Quantitative or qualitative results were reported for all prespecified outcomes (explicitly stated or inferred), exposure groups, and evaluation time points. Data not reported in the primary article is available from supplemental material. If results, omissions, or animal attrition are identified, the study authors provide an explanation, and these factors are not expected to impact the interpretation of the results. • *Adequate*: Quantitative or qualitative results are reported for most prespecified outcomes (explicitly stated or inferred), exposure groups, and evaluation time points. Omissions and/or attrition are not explained but are not expected to significantly impact the interpretation of the results. • *Deficient*: Quantitative or qualitative results are missing for many prespecified outcomes (explicitly stated or inferred), exposure groups and evaluation time points and/or high animal attrition; omissions and/or attrition are not explained and may significantly impact the interpretation of the results. • *Critically deficient*: Extensive results omission and/or animal attrition is identified and prevents comparisons of results across treatment groups.

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Table C-[SEQ Table_C- * ARABIC]. Questions Used to Guide the Development of Criteria for Each Domain in Experimental Animal Toxicology Studies

Evaluation Type	Domain– Core Question	Prompting Questions	Basic Considerations

Sensitivity
Exposure methods sensitivity
	Chemical administration and characterization–
	Did the study adequately characterize exposure to the chemical of interest and the exposure administration methods?
	Note:
	Consideration of the appropriateness of the route of exposure is not evaluated at the individual study level. Relevance and utility of the routes of exposure are considered in the PECO criteria for study inclusion and during evidence synthesis.
		For each study:
		• Does the study report the source, purity, and/or composition (e.g., identity and percent distribution of different isomers) of the chemical? If not, can the purity and/or composition be obtained from the supplier (e.g., as reported on the website)?
		• Was independent analytical verification of the test article purity and composition performed?
		• Did the study authors take steps to ensure the reported exposure levels were accurate?
		  ○ For inhalation studies: Were target concentrations confirmed using reliable analytical measurements in chamber air?
		  ○ For oral studies: If necessary, based on consideration of chemical-specific knowledge (e.g., instability in solution; volatility) and/or exposure design (e.g., the frequency and duration of exposure), were chemical concentrations in the dosing solutions or diet analytically confirmed?
		• Are there concerns about the methods used to administer the chemical (e.g., inhalation chamber type, gavage volume, etc.)?
			It is essential that these criteria are considered and potentially refined by assessment teams, as the specific variables of concern can vary by chemical.
			A judgment and rationale for this domain should be given for each cohort or experiment in the study.
			• *Good*: Chemical administration and characterization is complete (i.e., source, purity, and analytical verification of the test article are provided). There are no concerns about the composition, stability, or purity of the administered chemical or the specific methods of administration. For inhalation studies, chemical concentrations in the exposure chambers are verified using reliable analytical methods.
			• *Adequate*: Some uncertainties in the chemical administration and characterization are identified but these are expected to have minimal impact on interpretation of the results (e.g., source and vendor-reported purity are presented, but not independently verified; purity of the test article is suboptimal but not concerning). For inhalation studies, actual exposure concentrations are missing or verified with less reliable methods.
			• *Deficient*: Uncertainties in the exposure characterization are identified and expected to substantially impact the results (e.g., source of the test article is not reported, levels of impurities are substantial or concerning, deficient administration methods such as use of static inhalation chambers or a gavage volume considered too large for the species and/or life stage at exposure).
			• *Critically deficient*: Uncertainties in the exposure characterization are identified, and there is reasonable certainty that the results are largely attributable to factors other than exposure to the chemical of interest (e.g., identified impurities are expected to be a primary driver of the results).

Table C-[SEQ Table_C- * ARABIC]. Questions Used to Guide the Development of Criteria for Each Domain in Experimental Animal Toxicology Studies

Evaluation Type	Domain– Core Question	Prompting Questions	Basic Considerations
Sensitivity: Exposure methods sensitivity	**Exposure timing, frequency and duration–** Was the timing, frequency, and duration of exposure sensitive for the endpoint(s)/outcome(s) of interest?	For each endpoint/outcome or grouping of endpoints/outcomes in a study: • Does the exposure period include the critical window of sensitivity? • Was the duration and frequency of exposure sensitive for detecting the endpoint of interest?	Considerations for this domain are highly variable depending on the endpoint(s)/outcome(s) of interest and must be refined by assessment teams. A judgment and rationale for this domain should be given for each endpoint/outcome or group of endpoints/outcomes investigated in the study. • *Good*: The duration and frequency of the exposure was sensitive, and the exposure included the critical window of sensitivity (if known). • *Adequate*: The duration and frequency of the exposure was sensitive, and the exposure covered most of the critical window of sensitivity (if known). • *Deficient*: The duration and/or frequency of the exposure is not sensitive and did not include the majority of the critical window of sensitivity (if known). These limitations are expected to bias the results towards the null. • *Critically Deficient*: The exposure design was not sensitive and is expected to strongly bias the results towards the null. The rationale should indicate the specific concern(s).

Table C-[SEQ Table_C- * ARABIC]. Questions Used to Guide the Development of Criteria for Each Domain in Experimental Animal Toxicology Studies

Evaluation Type	Domain– Core Question	Prompting Questions	Basic Considerations
Sensitivity Outcome measures and results display	**Endpoint sensitivity and specificity–** Are the procedures sensitive and specific for evaluating the endpoint(s)/outcome(s) of interest? *Note:* *Sample size alone is not a reason to conclude an individual study is critically deficient.*	For each endpoint/outcome or grouping of endpoints/outcomes in a study: • Are there concerns regarding the specificity and validity of the protocols? • Are there serious concerns regarding the sample size (see note)? • Are there concerns regarding the timing of the endpoint assessment?	Considerations for this domain are highly variable depending on the endpoint(s)/outcome(s) of interest and must be refined by assessment teams. A judgment and rationale for this domain should be given for each endpoint/outcome or group of endpoints/outcomes investigated in the study. Examples of potential concerns include: • Selection of protocols that are insensitive or nonspecific for the endpoint of interest. • Use of unreliable methods to assess the outcome. • Assessment of endpoints at inappropriate or insensitive ages, or without addressing known endpoint variation (e.g., due to circadian rhythms, estrous cyclicity, etc.). • Decreased specificity or sensitivity of the response due to the timing of endpoint evaluation, as compared to exposure (e.g., short-acting depressant or irritant effects of chemicals, insensitivity due to prolonged period of nonexposure prior to testing).

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Table C-[SEQ Table_C- * ARABIC]. Questions Used to Guide the Development of Criteria for Each Domain in Experimental Animal Toxicology Studies

Evaluation Type	Domain– Core Question	Prompting Questions	Basic Considerations
Sensitivity: Outcome measures and results display	**Results presentation–** Are the results presented in a way that makes the data usable and transparent?	For each endpoint/outcome or grouping of endpoints/outcomes in a study: • Does the level of detail allow for an informed interpretation of the results? • Are the data analyzed, compared, or presented in a way that is inappropriate or misleading?	Considerations for this domain are highly variable depending on the outcomes of interest and must be refined by assessment teams. A judgment and rationale for this domain should be given for each endpoint/outcome or group of endpoints/outcomes investigated in the study. Examples of potential concerns include: • Nonpreferred presentation such as developmental toxicity data averaged across pups in a treatment group when litter responses are more appropriate. • Failure to present quantitative results. • Pooled data when responses are known or expected to differ substantially (e.g., across sexes or ages). • Failure to report on or address overt toxicity when exposure levels are known or expected to be highly toxic. • Lack of full presentation of the data (e.g., presentation of mean without variance data; concurrent control data are not presented).

Table C-[SEQ Table_C- * ARABIC]. Questions Used to Guide the Development of Criteria for Each Domain in Experimental Animal Toxicology Studies

Evaluation Type	Domain– Core Question	Prompting Questions	Basic Considerations
Overall Confidence	**Overall Confidence–** Considering the identified strengths and limitations, what is the overall confidence rating for the endpoint(s)/outcome(s) of interest? *Note:* *Reviewers should mark studies that are rated lower than high confidence only due to low sensitivity (i.e., bias towards the null) for additional consideration during evidence synthesis. If the study is otherwise well-conducted and an effect is observed, the confidence may be increased.*	For each endpoint/outcome or grouping of endpoints/outcomes in a study: • Were concerns (i.e., limitations or uncertainties) related to the reporting quality, risk of bias, or sensitivity identified? • If yes, what is their expected impact on the overall interpretation of the reliability and validity of the study results, including (when possible) interpretations of impacts on the magnitude or direction of the reported effects?	The overall confidence rating considers the likely impact of the noted concerns (i.e., limitations or uncertainties) in reporting, bias, and sensitivity on the results. A confidence rating and rationale should be given for each endpoint/outcome or group of endpoints/outcomes investigated in the study. • *High confidence*: No notable concerns are identified (e.g., most or all domains rated *good*). • *Medium confidence*: Some concerns are identified, but expected to have minimal impact on the interpretation of the results (e.g., most domains rated *adequate* or *good*; may include studies with *deficient* ratings if concerns are not expected to strongly impact the magnitude or direction of the results). Any important concerns should be carried forward to evidence synthesis. • *Low confidence*: Identified concerns are expected to significantly impact the study results or their interpretation (e.g., generally, *deficient* ratings for one or more domains). The concerns leading to this confidence judgment must be carried forward to evidence synthesis (see note). • *Uninformative*: Serious flaw(s) that make the study results unusable for informing hazard identification (e.g., generally, *critically deficient* rating in any domain; many *deficient* ratings). *Uninformative* studies are considered no further in the synthesis and integration of evidence.

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Table C-[SEQ Table_C- * ARABIC]. Questions Used to Guide the Development of Criteria for Each Domain in Experimental Animal Toxicology Studies			
Evaluation Type	**Domain–Core Question**	**Prompting Questions**	**Basic Considerations**

[a]For nontargeted or screening-level histopathology outcomes often used in guideline studies, blinding during the initial evaluation of tissues is generally not recommended because masked evaluation can make "the task of separating treatment-related changes from normal variation more difficult" and "there is concern that masked review during the initial evaluation may result in missing subtle lesions." Generally, blinded evaluations are recommended for targeted secondary review of specific tissues or in instances when there is a predefined set of outcomes that is known or predicted to occur [ADDIN EN.CITE <EndNote><Cite><Author>Crissman</Author><Year>2004</Year><RecNum>1025</RecNum><IDText>51763</IDText><DisplayText>(Crissman et al., 2004)</DisplayText><record><rec-number>1025</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957800">1025</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Crissman, J. W.</author><author>Goodman, D. G.</author><author>Hildebrandt, P. K.</author><author>Maronpot, R. R.</author><author>Prater, D. A.</author><author>Riley, J. H.</author><author>Seaman, W. J.</author><author>Thake, D. C.</author></authors></contributors><titles><title>Best practices guideline: Toxicologic histopathology</title><secondary-title>Toxicologic Pathology</secondary-title><alt-title>Toxicol Pathol</alt-title><short-title>Toxicologic Pathology</short-title></titles><periodical><full-title>Toxicologic Pathology</full-title><abbr-1>Toxicol Pathol</abbr-1></periodical><alt-periodical><full-title>Toxicologic Pathology</full-title><abbr-1>Toxicol Pathol</abbr-1></alt-periodical><pages>126-131</pages><volume>32</volume><dates><year>2004</year></dates><isbn>ISSN 0192-6233
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GLP = Good Laboratory Practice; OECD = Organisation for Economic Cooperation and Development.

APPENDIX D. HAWC USER GUIDE AND FREQUENTLY ASKED QUESTIONS

D.1 WHAT IS HAWC AND WHAT IS ITS PURPOSE?

The Health Assessment Workspace Collaborative (HAWC) is an interactive, expert-driven, content management system for human health assessments that is intended to promote transparency, trackability, data usability, and understanding of the data and decisions supporting an environmental and human health assessment. Specifically, HAWC is an interface that allows the data and decisions supporting an assessment to be managed in modules (e.g., study evaluation, summary study data, etc.) that can be publicly accessed online (see Section D.2 below and [REF _Ref55819003 \h]). Following the literature search and screening that are conducted using [HYPERLINK "https://hero.epa.gov/hero/index.cfm/project/page/project_id/2610"] and [HYPERLINK "https://www.evidencepartners.com/products/distillersr-systematic-review-software"], HAWC manages each study included in an assessment and makes the extracted information available via a web link that takes a user to a web page displaying study-specific details and data (e.g., study evaluation, experimental design, dosing regime, endpoints evaluated, dose-response data, etc., described in further detail below in Sections D.3 to D.6). Finally, all data managed in HAWC is fully downloadable using the blue "Download datasets" link (highlighted in the red box below) also located in the gray navigation bar located on the assessment home page (discussed in Section D.7). Note that a user may quickly navigate HAWC by clicking on the file path (highlighted in the orange, dashed box below) given in the gray row below the HAWC icon and menu bar (see [REF _Ref55819003 \h]). HAWC aims to facilitate team collaboration by scientists who develop these assessments and enhance transparency of the process by providing online access (no user account required) to the data and expert decisions used to evaluate potential human health hazard and risk of chemical exposures.

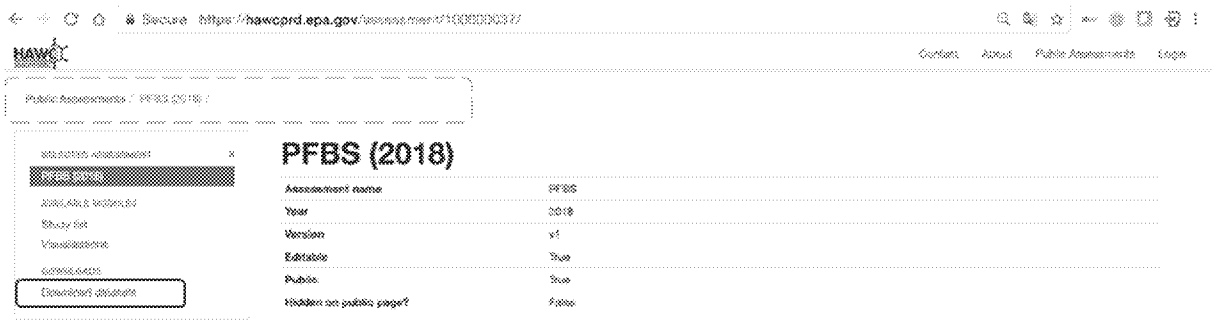

Figure D-[SEQ Figure_D- * ARABIC]. HAWC Homepage for the Public PFBS Assessment

D.2 HOW DO I ACCESS HAWC?

HAWC is an open-source, online application that may be accessed using the following link—[HYPERLINK "https://hawcprd.epa.gov/assessment/public/"]—and then selecting an available assessment. The following browsers are fully supported for accessing HAWC: Google Chrome (preferred), Mozilla Firefox, and Apple Safari. There are errors in functionality when

viewed with Internet Explorer. No user account is required for access to public HAWC assessments. The assessments located in HAWC are meant to accompany a textual expert synthesis of the data managed in HAWC. Each written assessment document contains embedded URL links to the evidence in HAWC (e.g., study evaluation, summary study data, visualizations, etc.) supporting the assessment text. The links embedded in an assessment document can be accessed by a mouse click (or hover while pressing CTRL + right click).

D.3 WHAT CAN I FIND IN HAWC?

HAWC contains a comprehensive landscape of study details and data supporting an assessment. Note that links are provided in the assessment text to guide the reader, but a user may also navigate to the HAWC homepage for an assessment on their own. Once a user lands on an [HYPERLINK "https://hawcprd.epa.gov/assessment/100000037/"], all studies included in an assessment can be viewed by clicking the blue "[HYPERLINK "https://hawcprd.epa.gov/study/assessment/100000037/"]" link (highlighted in the red box below) in the gray navigation pane (see [REF _Ref55819023 \h]). By clicking the study name listed in blue (under "Short citation") a user can view the full study details, study evaluation, and experimental details and data. For example, in [REF _Ref55819023 \h], a user may click on "3M, 2000, 4289992" (highlighted in the orange, dashed box below). This will take the user to the [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=4289992"] study details page that includes a link to the study in [HYPERLINK "https://hero.epa.gov/hero/index.cfm/reference/details/reference_id/4289992"] along with study details, study evaluation, and available experimental (animal) and study population (epidemiologic) groups.

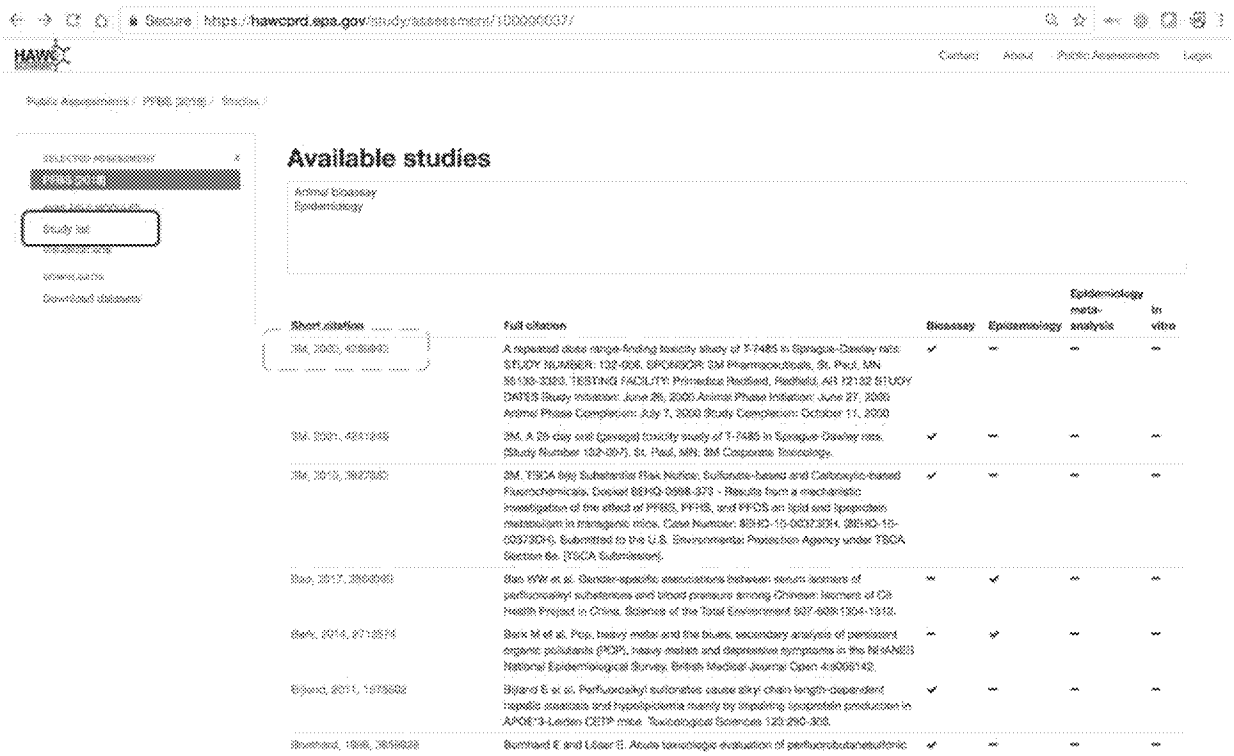

Figure D-[SEQ Figure_D- * ARABIC]. Representative Study List

D.4 HOW DO I ACCESS STUDY EVALUATION(S)?

Study evaluation is performed to ensure that the studies used in the assessment are conducted in such a manner that the results are credible for each outcome and the ratings are outcome specific. The study evaluation criteria and decisions are fully documented in HAWC and displayed for each study on the study details page. Study evaluation is depicted as a pie chart with each domain and rating making up a piece of the pie that is colored according to the rating. A user may hover over each piece of the pie, which causes rating metric text to populate to the right of the pie graph (see [REF _Ref55819049 \h]). For full domain and rating details the user may click the blue "[HYPERLINK "https://hawcprd.epa.gov/rob/study/100001452/"]" button (highlighted in the red box below). [Note that this example is given for the [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=4289992"]].

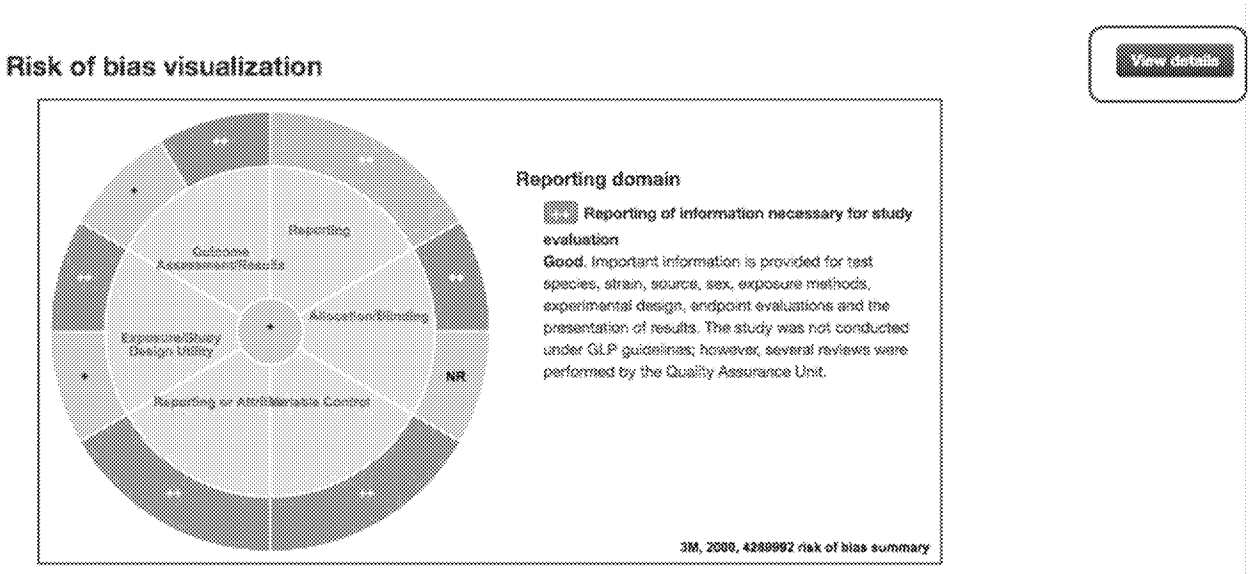

Figure D-[SEQ Figure_D- * ARABIC]. Representative Study Evaluation Pie Chart with the Reporting Domain Selected and Text Populating to the Right of Pie Chart

D.5 HOW DO I ACCESS STUDY-SPECIFIC INFORMATION ON EXPERIMENTAL AND STUDY POPULATION DETAILS AND EXTRACTED ENDPOINT DATA?

Specific information on experimental design, dosing (if animal bioassay), outcomes and exposure (if epidemiology), and extracted endpoint data can be accessed from the study details page by clicking on [for the [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=4289992"] study][HYPERLINK "https://hawcprd.epa.gov/study/100001452/"]" at the bottom of the study details page. A user may click on the experiment name (highlighted in blue, [HYPERLINK "https://hawcprd.epa.gov/ani/experiment/100000155/"]) to view dosing/exposure details and available groups. Clicking on available animal groups (e.g., [HYPERLINK "https://hawcprd.epa.gov/ani/animal-group/100000419/"] or [HYPERLINK "https://hawcprd.epa.gov/ani/animal-group/100000420/"]) will take the reader to a new page with experimental group information (e.g., species/strain/sex, dosing regimen information, and available/additional endpoints information for animal studies; and outcome and exposure information for epidemiologic studies). If a study reports data, then the data are extracted and managed as "available endpoints." If the study authors include endpoints in the methods and results but do not report data, the endpoint is listed under "additional endpoints" without dose-response data. All endpoints are also clickable and contain an endpoint description, methods, and (if data are reported) a clickable data plot (e.g., [HYPERLINK "https://hawcprd.epa.gov/ani/endpoint/100002666/"]). The description of endpoints, methods, and data are often copied directly from the study report and, therefore, can contain study author judgments and may not necessarily include U.S. EPA judgments on the endpoint data that would be included in the assessment.

D.6 WHAT ARE VISUALIZATIONS AND HOW DO I ACCESS THEM?

The data managed in HAWC is displayed using visualizations that are intended to support textual descriptions within an assessment. All visualizations can be accessed using the

blue "[HYPERLINK "https://hawcprd.epa.gov/summary/assessment/100000037/visuals/"]" link (highlighted in the red box below) also found in the gray navigation pane (see [REF _Ref55819067 \h]A). *Note that the available visualizations are at the discretion of the chemical manager and are meant to accompany the assessment text.* Visualizations are fully interactive. Hovering and clicking on records in the rows and columns and data points on a plot will cause a pop-up window to appear (see [REF _Ref55819114 \h]B). This pop-up window is also interactive and clicking on blue text within this pop-up will open a new web page with descriptive data.

Figure D-[SEQ Figure_D- * ARABIC]A. Visualization Example for PFBS (Note that the records listed under each column [study, experiment endpoint, units, study design, observation time, dose] and data within the plot are interactive.)

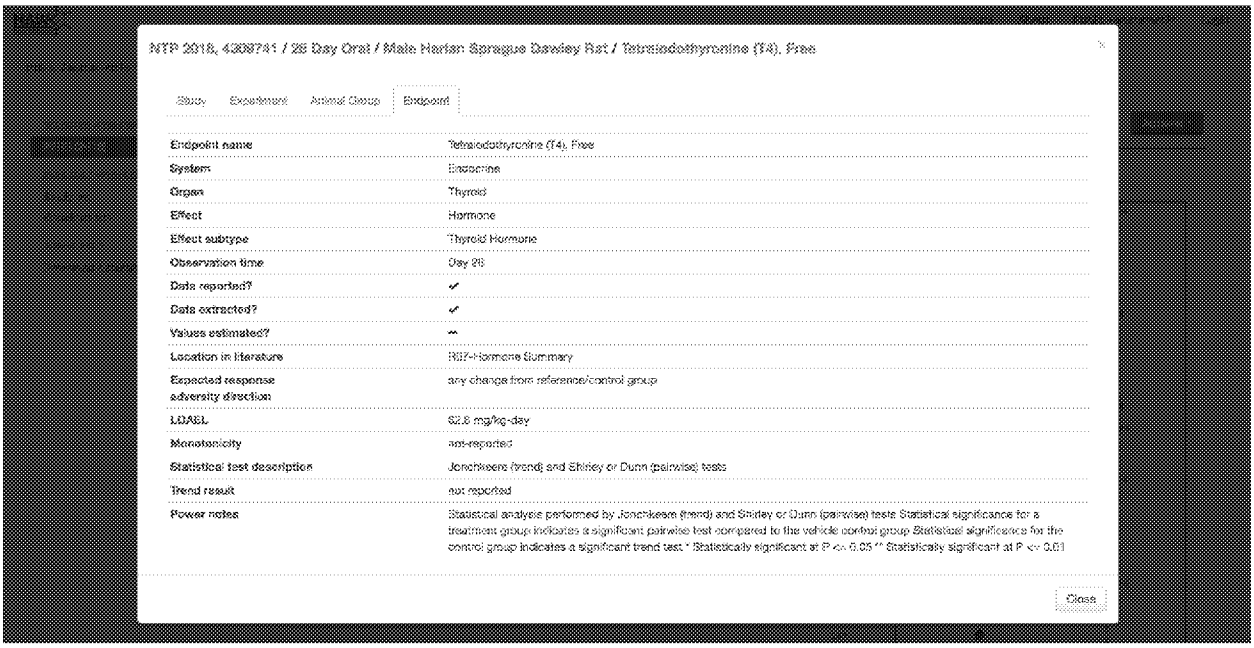

Figure D-[SEQ Figure_D- * ARABIC]B. Example Pop-Up Window after Clicking on Interactive Visualization Links

(In [REF _Ref55819067 \h]A, the red circle for study [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5400978"]; male at a dose of 500 mg/kg-day was clicked leading to the pop-up shown above. Clicking on the blue text will open a new window with descriptive data.)

D.7 HOW DO I DOWNLOAD DATA SETS?

A user may download any available data set by first clicking on the blue "[HYPERLINK "https://hawcprd.epa.gov/assessment/100000037/downloads/"]" link (highlighted in the red box below) in the gray navigation pane on the assessment homepage. This takes the user to a new page where the desired data set may be selected for download as an Excel file (see representative image in [REF _Ref55819184 \h]).

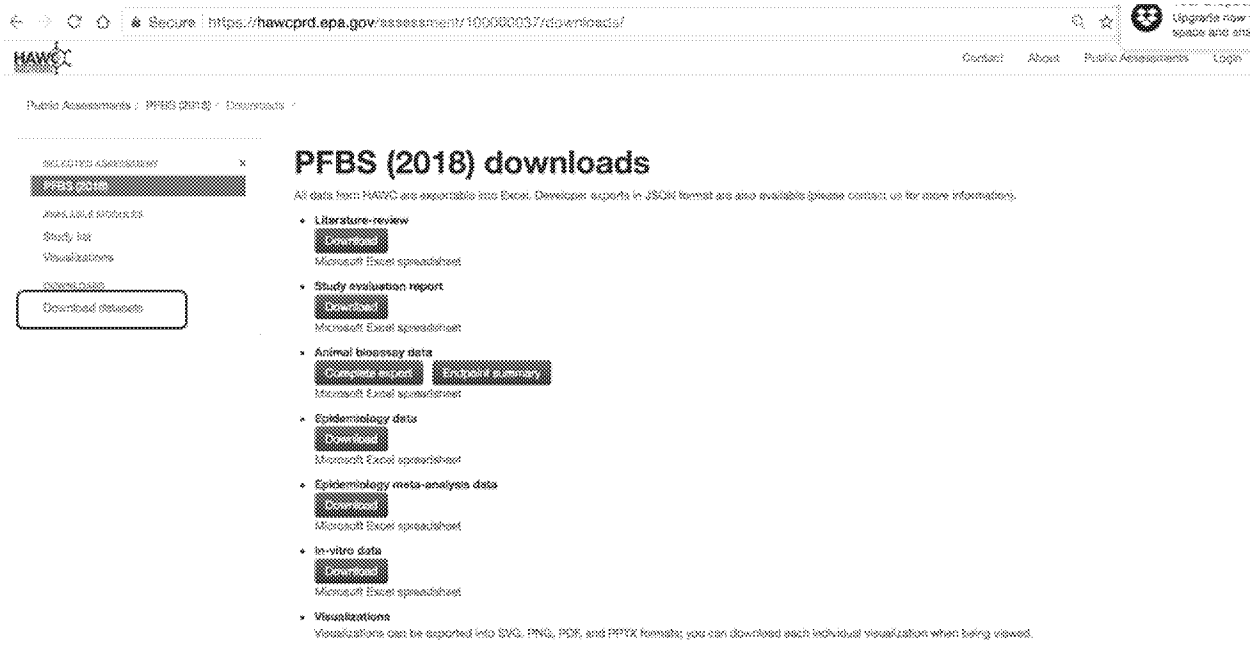

Figure D-[SEQ Figure_D- * ARABIC]. Representative Data Download Page

D.8 HOW DO I ACCESS THE BENCHMARK DOSE MODELING OUTPUTS?

Benchmark dose (BMD) modeling is performed on an endpoint-by-endpoint basis at the discretion of the chemical manager. Those endpoints for which BMD modeling has been completed are referenced in the assessment text and are available for viewing. To access BMD modeling outputs the user can click on links included in the assessment text. Alternatively, the user may navigate to the BMD modeling outputs by clicking on a study [e.g., [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"]] of interest from the [HYPERLINK "https://hawcprd.epa.gov/study/assessment/100000037/"], an available animal bioassay experiment (in this example, the [HYPERLINK "https://hawcprd.epa.gov/ani/experiment/100000108/"] study), an available animal group ([HYPERLINK "https://hawcprd.epa.gov/ani/animal-group/100000287/"]), and an endpoint of interest ([HYPERLINK "https://hawcprd.epa.gov/ani/endpoint/100002285/"]). Next navigate

to the blue "Actions" button, click, and scroll to "[HYPERLINK "https://hawcprd.epa.gov/bmd/session/100000019/"]" (highlighted in the red box below) under BMD Modeling (see [REF _Ref55819207 \h]A). The [HYPERLINK "https://hawcprd.epa.gov/bmd/session/100000019/" \l "setup"], [HYPERLINK "https://hawcprd.epa.gov/bmd/session/100000019/" \l "results"], and [HYPERLINK "https://hawcprd.epa.gov/bmd/session/100000019/" \l "recommendations"] (highlighted in the orange, dashed box in [REF _Ref55819222 \h]B) are available for viewing. Selecting the BMD setup tab will display the modeled dose-response data, the selected models and options, and all benchmark modeling responses (BMRs). The results tab will display the BMD modeling output summary for all models. A user may hover over a selected model row to visualize the model fit to the data. In addition, a user may obtain the Benchmark Dose Software (BMDS) output text by clicking the "View" button under the "Output" column for each model that was run. The "Model recommendation and selection" tab displays all models, warnings when appropriate, and the recommendation for which models are valid, questionable, or failed to fit.

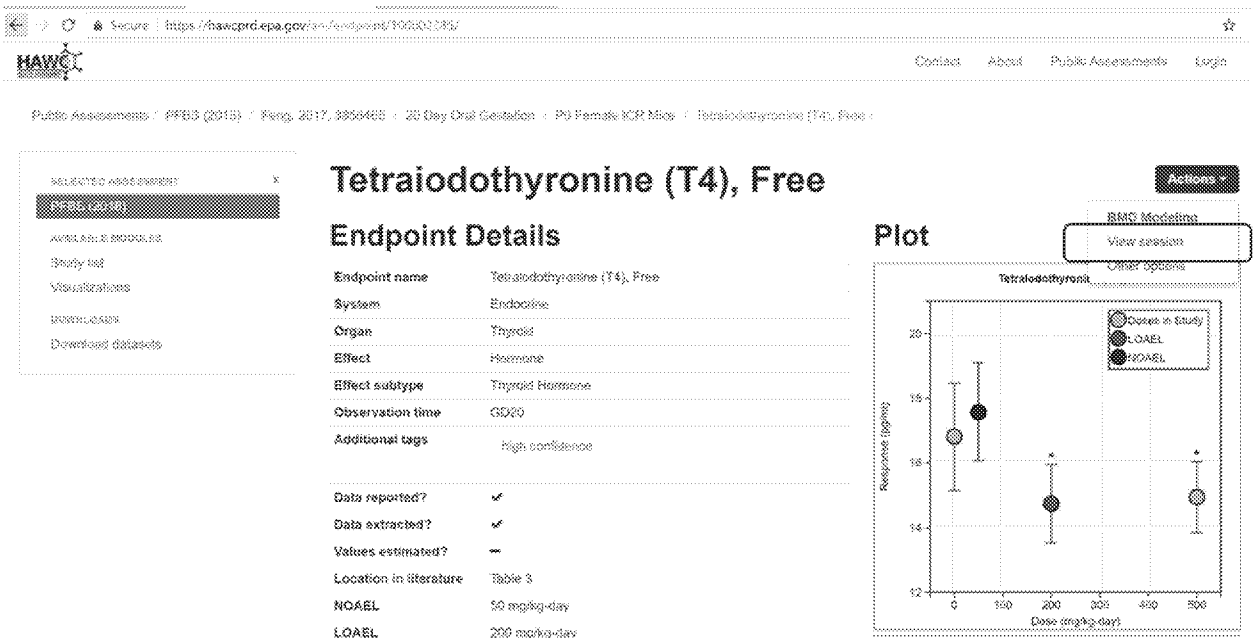

Figure D-[SEQ Figure_D- * ARABIC]A. Example BMD Modeling Navigation

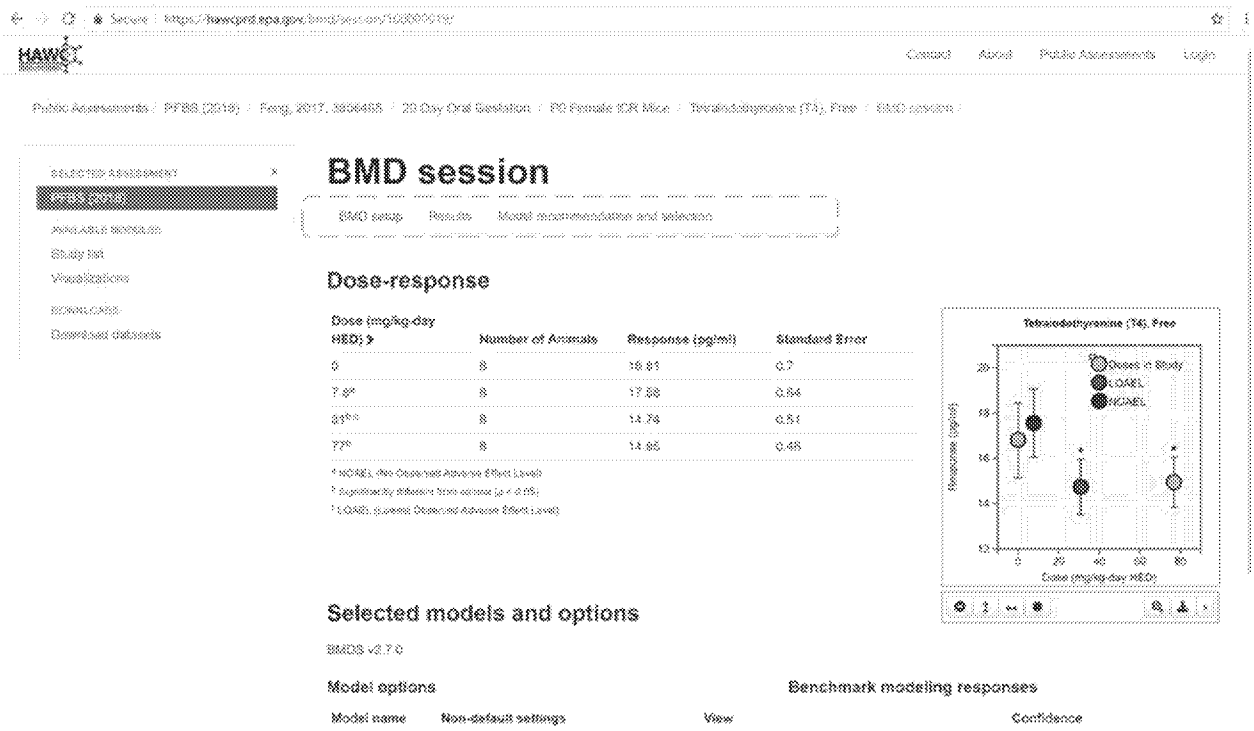

Figure D-[SEQ Figure_D- * ARABIC]B. Example BMD Session

APPENDIX E. ADDITIONAL DATA FIGURES

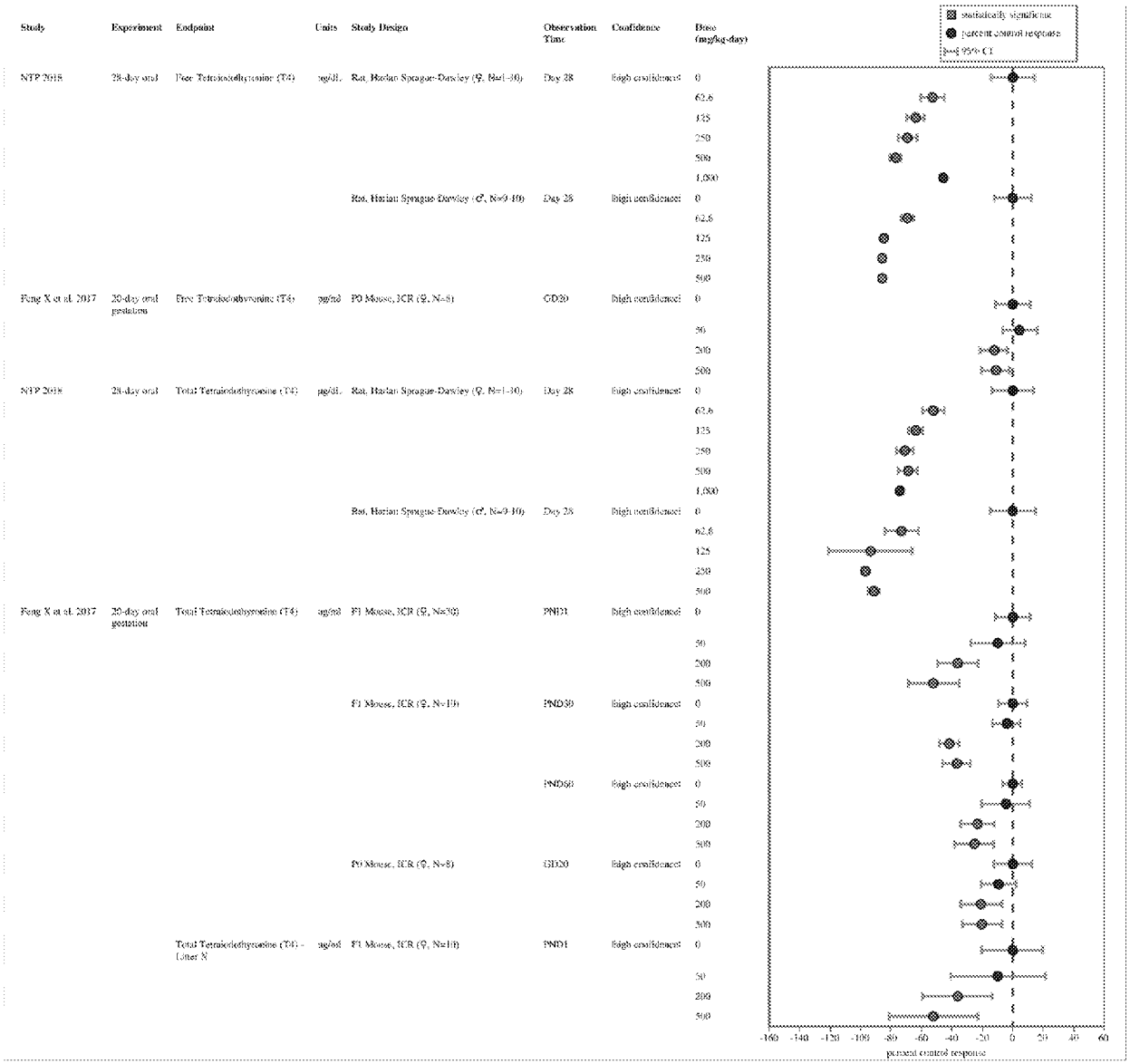

Figure E-[SEQ Figure_E- * ARABIC]. Serum Free and Total Thyroxine (T_4) Response in Animals Following K^+PFBS Exposure
(Click to see [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-t4-effect-size-animal/"])

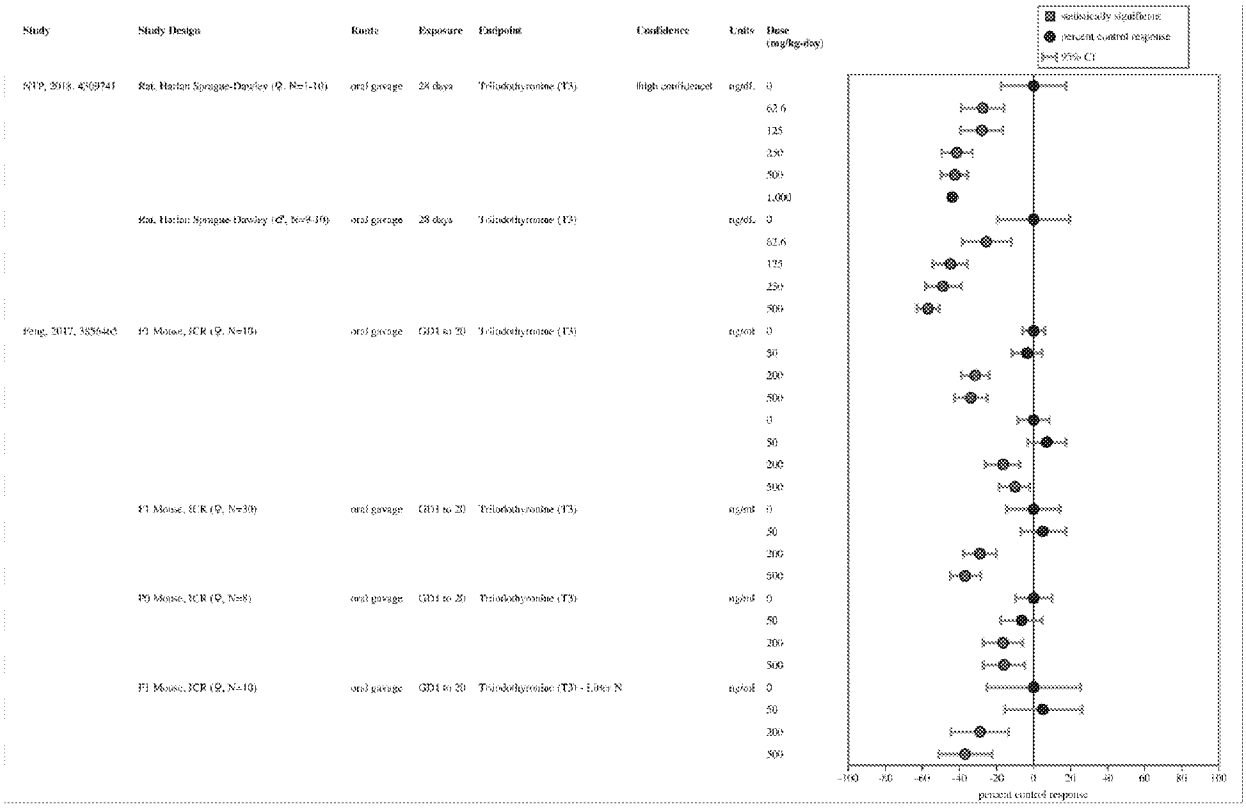

Figure E-[SEQ Figure_E- * ARABIC]. Serum Total Triiodothyronine (T_3) Response in Animals Following K^+PFBS Exposure
(Click to see [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-t3-effect-size-animal/"])

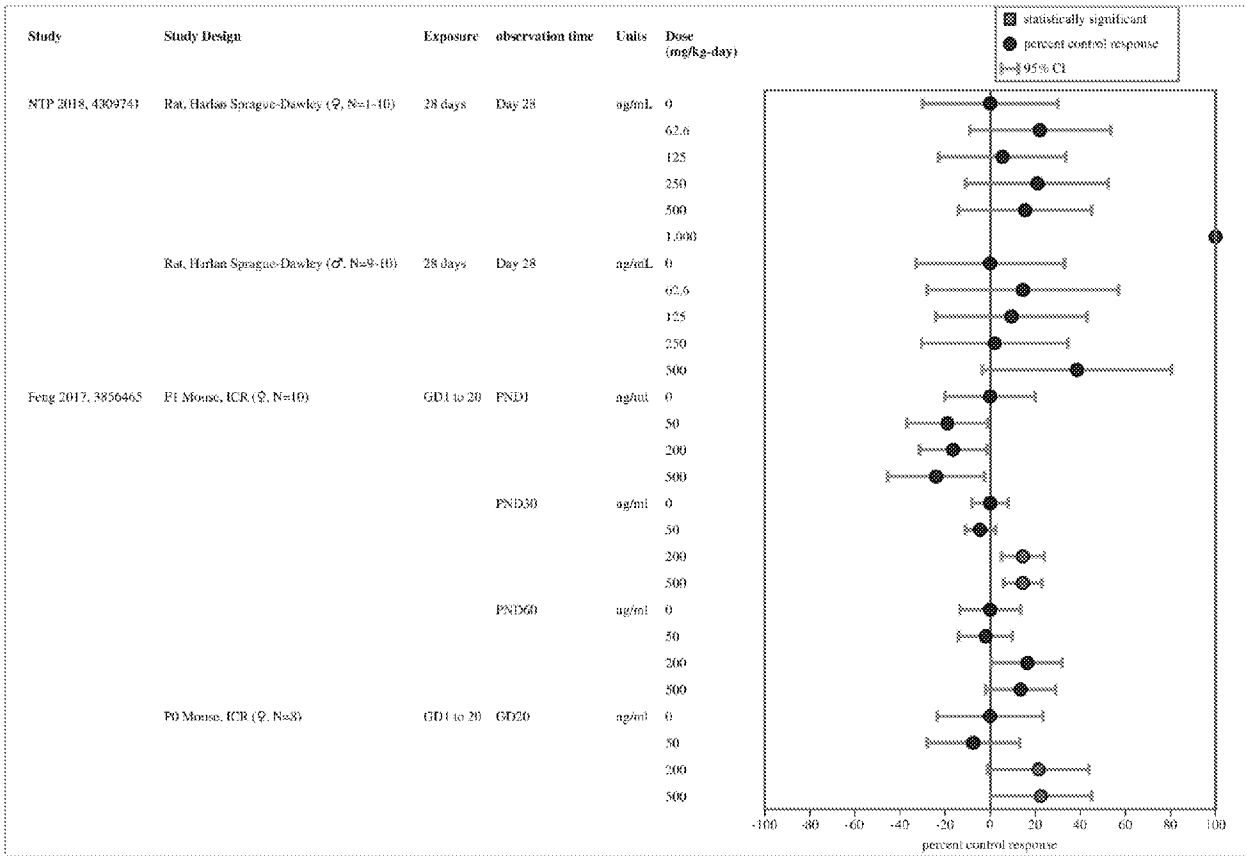

Figure E-[SEQ Figure_E- * ARABIC]. Serum Thyroid-Stimulating Hormone (TSH) Response in Animals Following K^+PFBS Exposure
(Click to see [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-tsh-effect-size-animal/"])

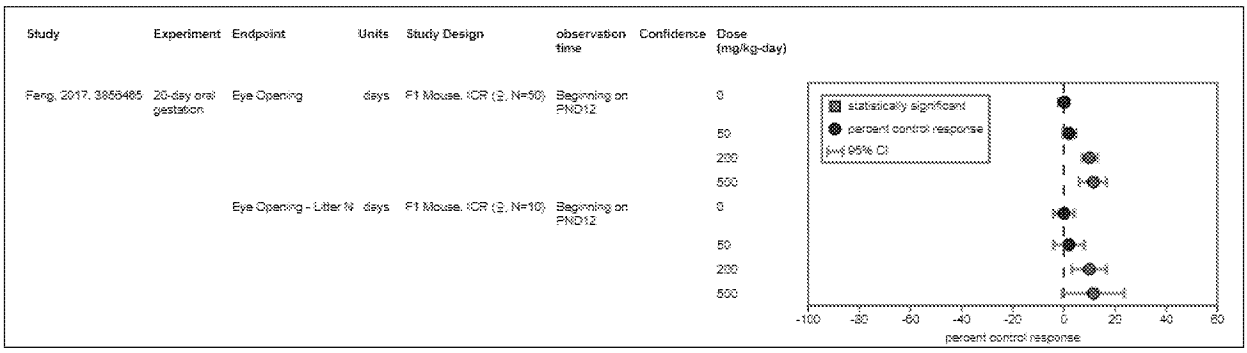

Figure E-[SEQ Figure_E- * ARABIC]. Developmental Effects (Eye Opening) Following K^+PFBS Exposure in Rats
(Click to see [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-eye-opening-effect-size-animal/"])

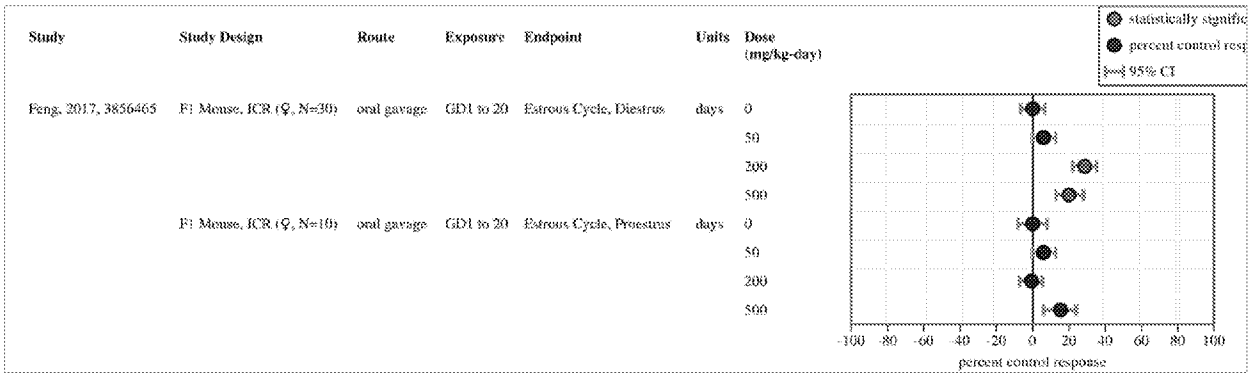

Figure E-[SEQ Figure_E- * ARABIC]. Developmental Effects (First Estrus) Following K^+PFBS Exposure in Rats
(Click to see [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-estrous-cyclicity-effect-size-animal/"])

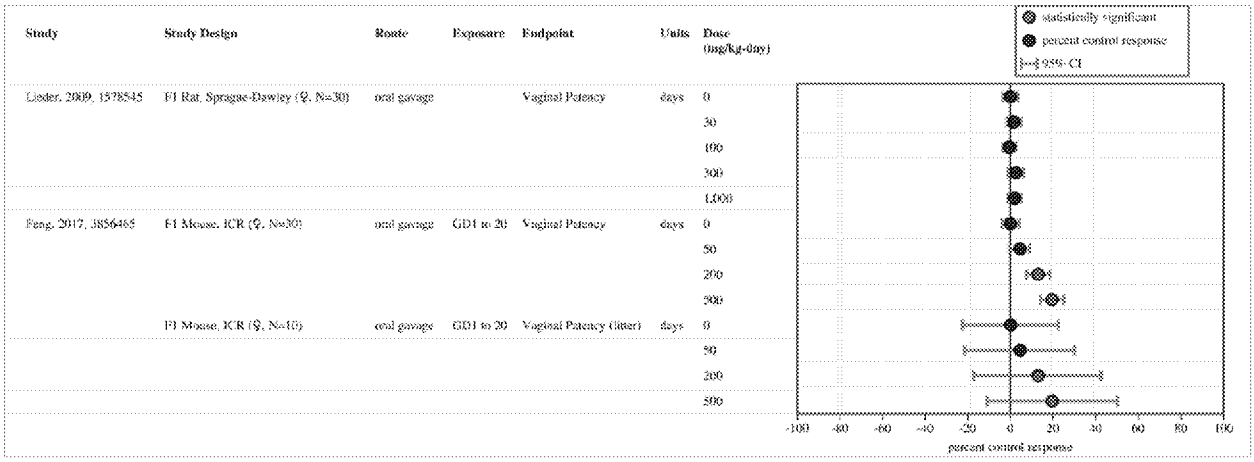

Figure E-[SEQ Figure_E- * ARABIC]. Developmental Effects (Vaginal Patency) Following K^+PFBS Exposure in Rats
(Click to see [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-vaginal-opening-effect-size-animal/"])

Figure E-[SEQ Figure_E- * ARABIC]. Kidney Histopathological Effects Following K^+PFBS Exposure in Rats
(Click to see [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-kidney-histopathology-effect-size-animal/"])

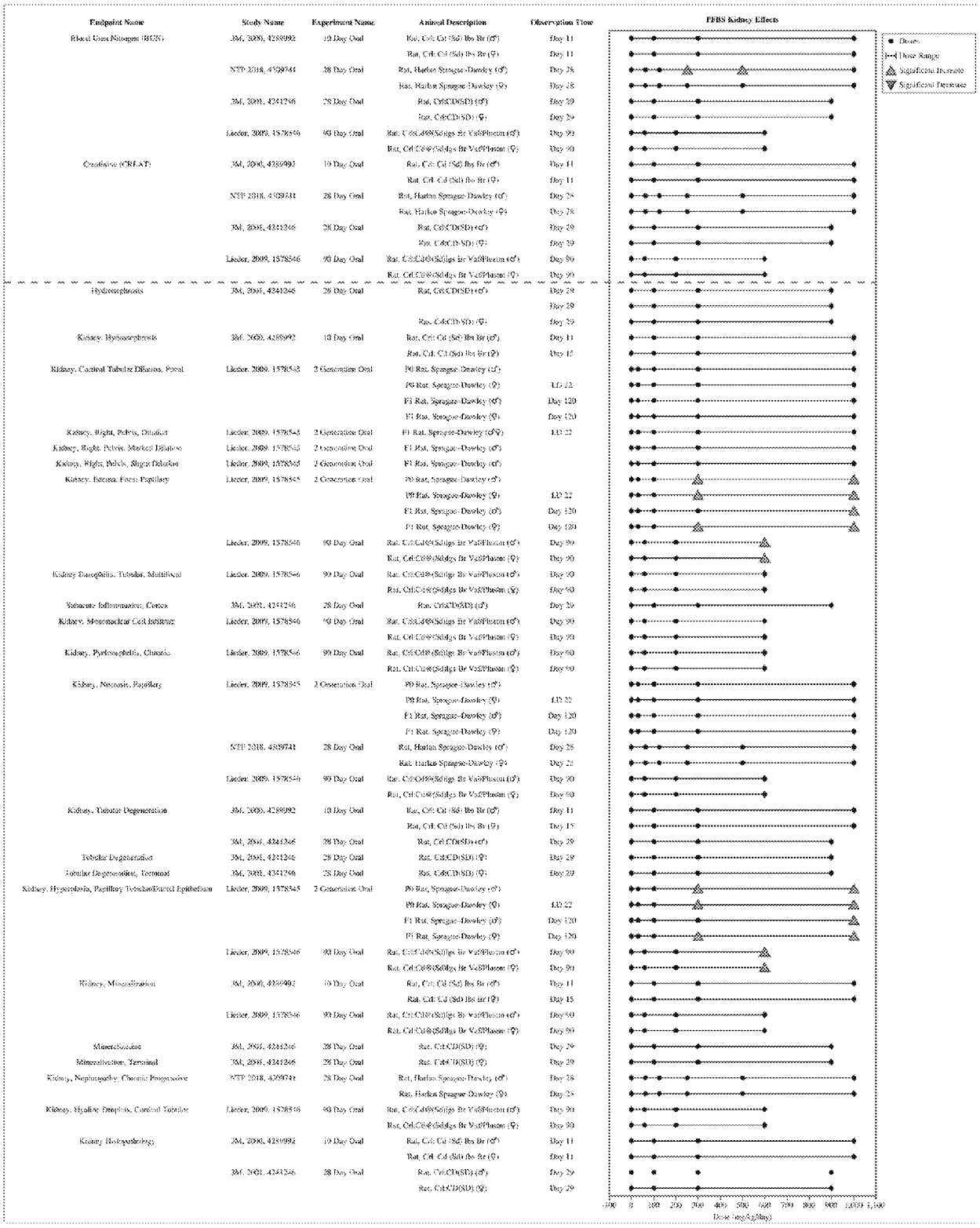

Figure E-[SEQ Figure_E- * ARABIC]. Renal Effects Following K^+PFBS Exposure in Rats

(Click to see [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-kidney-effects-kris-v3/"])

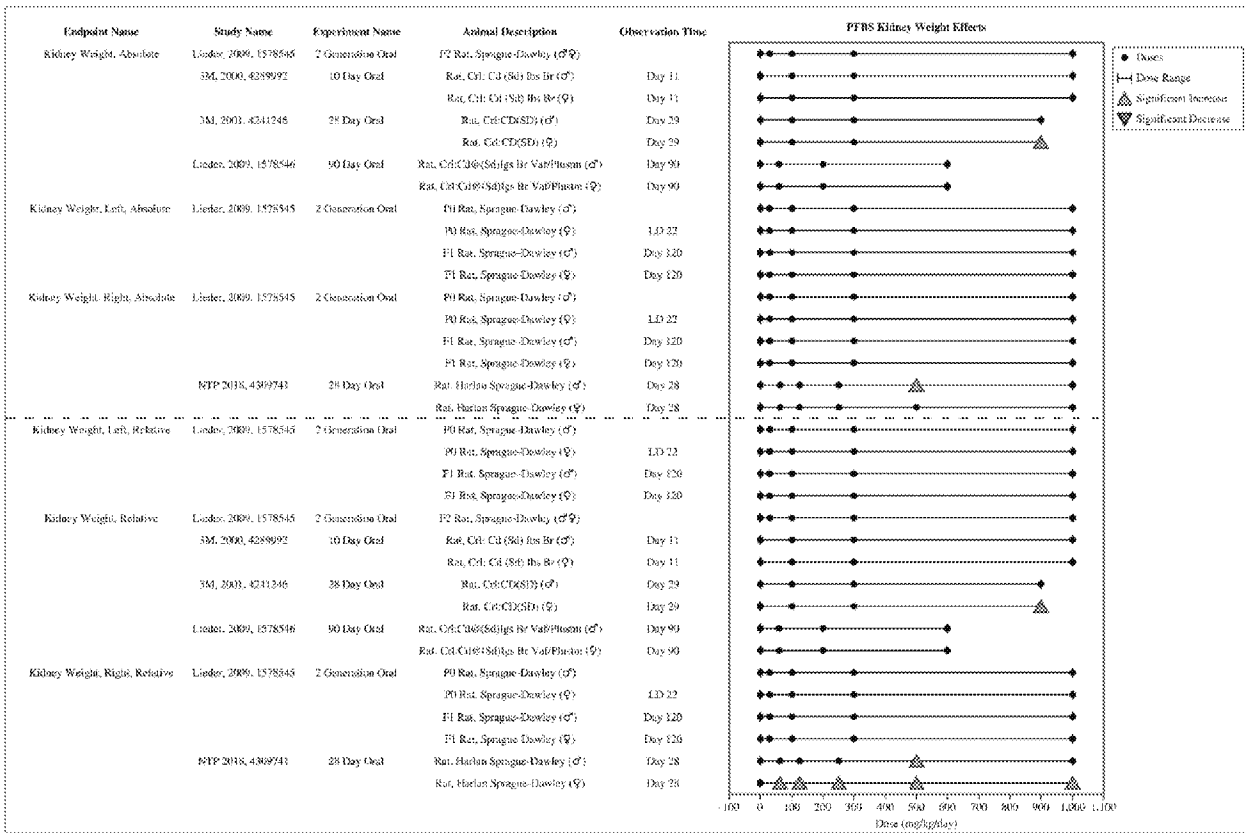

Figure E-[SEQ Figure_E- * ARABIC]. Kidney-Weight Effects Following K^+PFBS Exposure in Rats
(Click to see [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-kidney-effects-kris-v3/"])

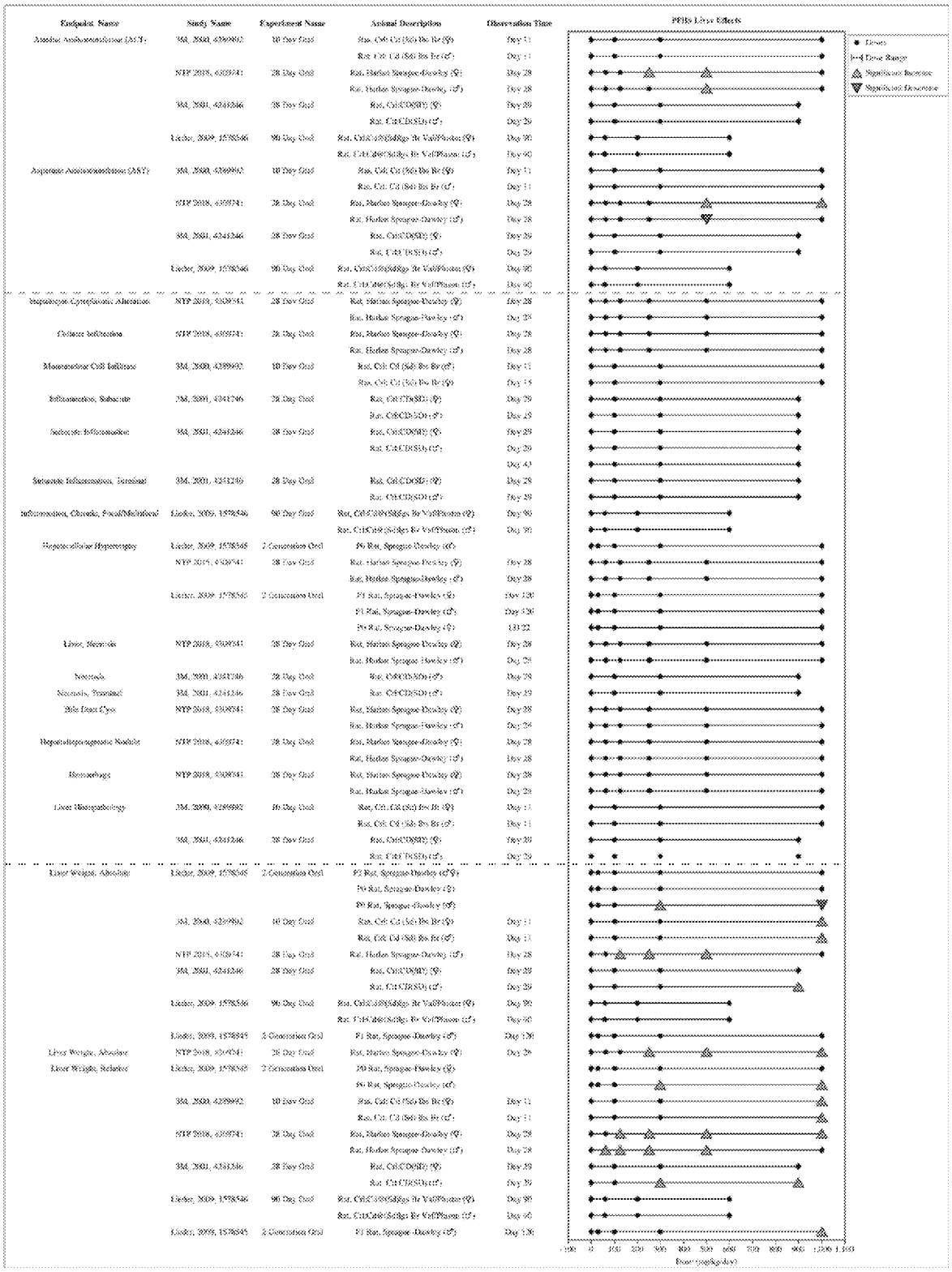

Figure E-[SEQ Figure_E- * ARABIC]. Liver Effects Following K^+PFBS Exposure in Rats (Click to see [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-liver-effects/"])

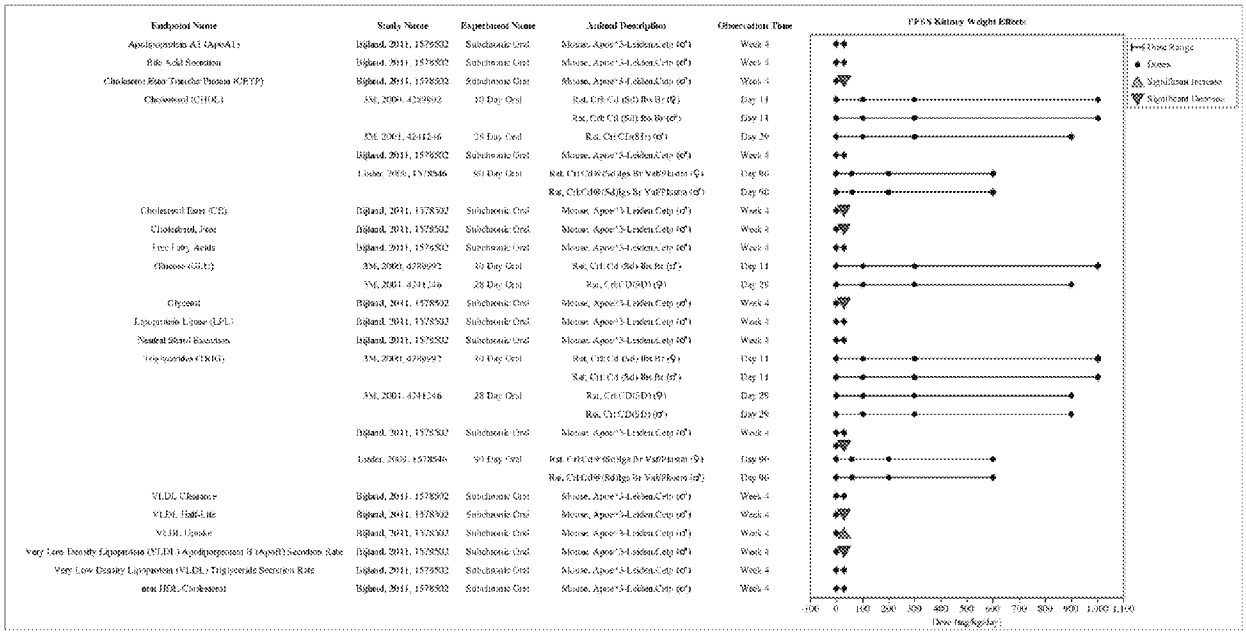

Figure E-[SEQ Figure_E- * ARABIC]. Effects on Lipids and Lipoproteins Following K^+PFBS Exposure in Rats and Mice
(Click to see [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-lipid-effects/"])

APPENDIX F. BENCHMARK DOSE MODELING RESULTS

F.1. MODELING OF NONCANCER ENDPOINTS

As discussed in the body of the report under "Derivation of Oral Reference Doses," the endpoints selected for benchmark dose (BMD) modeling were incidence of renal papillary epithelial tubular/ductal hyperplasia in rats from [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578546"] and [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578545"]; thyroid hormones in pregnant mice and offspring at Postnatal Days (PNDs) 1, 30, and 60 from [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"] and adult rats from [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5400978"]; and developmental effects (i.e., eye opening, first estrus, vaginal opening) from [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"]. The animal doses in the study, converted to human equivalent doses (HEDs), were used in the BMD modeling; the data are available for download in Health Assessment Workspace Collaborative (HAWC). BMD modeling was conducted by experts in quantitative Benchmark Dose Software (BMDS) analysis and interpretation. Links to the data and modeling output are included in [REF _Ref55817942 \h]. The selected point of departure (POD) (HED) listed in [REF _Ref55817942 \h] represents the best-fitting model for each endpoint; if the data were determined not to be amenable to BMD modeling, the no-observed-adverse-effect level (NOAEL) or lowest-observed-adverse-effect level (LOAEL) is listed. [REF _Ref55819534 \h] illustrates the doses examined and NOAEL, LOAEL, BMD, and benchmark dose lower confidence limit (BMDL) values for the potential critical effects.

Table F-[SEQ Table_F- * ARABIC]. Candidate PODs for the Derivation of the Subchronic and Chronic RfDs for PFBS (CASRN 375-73-5) and the Related Compound K^+PFBS (CASRN 29420-49-3)

Endpoint/Reference	Species/Life Stage—Sex	Selected POD (HED)[a] (mg/kg-d)
Kidney effects		
Kidney histopathology—papillary epithelial tubular/ductal hyperplasia—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578546"]	Rat—male	[HYPERLINK "https://hawcprd.epa.gov/bmd/session/100000008/"] = 0.489
	Rat—female	[HYPERLINK "https://hawcprd.epa.gov/bmd/session/100000010/"]
Kidney histopathology—papillary epithelial tubular/ductal hyperplasia—[HYPERLINK	Rat/P_0—male	[HYPERLINK "https://hawcprd.epa.g

Table F-[SEQ Table_F- * ARABIC]. Candidate PODs for the Derivation of the Subchronic and Chronic RfDs for PFBS (CASRN 375-73-5) and the Related Compound K^+PFBS (CASRN 29420-49-3)		
Endpoint/Reference	**Species/Life Stage—Sex**	**Selected POD (HED)[a] (mg/kg-d)**
"https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578545"]		ov/bmd/session/100000040/"]
	Rat/P_0—female	[HYPERLINK "https://hawcprd.epa.gov/bmd/session/100000048/"]
Kidney histopathology—papillary epithelial tubular/ductal hyperplasia—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=1578545"]	Rat/F_1—male	[HYPERLINK "https://hawcprd.epa.gov/bmd/session/100000042/"]
	Rat/F_1—female	[HYPERLINK "https://hawcprd.epa.gov/bmd/session/100000043/"]
Thyroid effects		
Total T_4—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5400978"]	Rat—male	[HYPERLINK "https://hawcprd.epa.gov/bmd/session/100000056/"]
	Rat—female	[HYPERLINK "https://hawcprd.epa.gov/bmd/session/100000050/"]
Free T_4—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5400978"]	Rat—male	[HYPERLINK "https://hawcprd.epa.gov/bmd/session/100000055/"]
	Rat—female	[HYPERLINK "https://hawcprd.epa.gov/bmd/session/100000052/"]
Total T_4—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"]	Mouse/P_0—female	[HYPERLINK "https://hawcprd.epa.gov/bmd/session/100000078/"]
Free T_4—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"]	Mouse/P_0—female	[HYPERLINK "https://hawcprd.epa.gov/bmd/session/100000019/"]
TSH—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"]	Mouse/P_0—female	[HYPERLINK "https://hawcprd.epa.gov/bmd/session/100000022/"]

Table F-[SEQ Table_F- * ARABIC]. Candidate PODs for the Derivation of the Subchronic and Chronic RfDs for PFBS (CASRN 375-73-5) and the Related Compound K^+PFBS (CASRN 29420-49-3)		
Endpoint/Reference	**Species/Life Stage—Sex**	**Selected POD (HED)[a] (mg/kg-d)**
Total T_4 PND 1 (fetal *n*)[b]—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"]	Mouse/F_1—female	[HYPERLINK "https://hawcprd.epa.gov/bmd/session/100000057/"]
Total T_4 PND 1 (litter *n*)[b]—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"]	**Mouse/F_1—female**	**[HYPERLINK "https://hawcprd.epa.gov/bmd/session/100000027/"] ($BMDL_{1SD}$ = 0.25)**
Total T_4 PND 30—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"]	Mouse/F_1—female	[HYPERLINK "https://hawcprd.epa.gov/bmd/session/100000036/"]
Total T_4 PND 60—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"]	Mouse/F_1—female	[HYPERLINK "https://hawcprd.epa.gov/bmd/session/100000037/"]
TSH PND 30—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"]	Mouse/F_1—female	[HYPERLINK "https://hawcprd.epa.gov/bmd/session/100000038/"]
Developmental effects		
Eyes opening (fetal *n*)[b]—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"]	Mouse/F_1—female	[HYPERLINK "https://hawcprd.epa.gov/bmd/session/100000083/"]
Eyes opening (litter *n*)[b]—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"]	Mouse/F_1—female	[HYPERLINK "https://hawcprd.epa.gov/bmd/session/100000024/"] ($BMDL_{1SD}$ = 0.16)
Vaginal opening (fetal *n*)[b]—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"]	Mouse/F_1—female	[HYPERLINK "https://hawcprd.epa.gov/bmd/session/100000026/"] ($BMDL_{1SD}$ = 0.35)
Vaginal opening (litter *n*)[b]—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"]	Mouse/F_1—female	[HYPERLINK "https://hawcprd.epa.gov/bmd/session/100000026/"] ($BMDL_{1SD}$ = 0.22)
First estrous (fetal *n*)[b]—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"]	Mouse/F_1—female	[HYPERLINK "https://hawcprd.epa.g

Table F-[SEQ Table_F- * ARABIC]. Candidate PODs for the Derivation of the Subchronic and Chronic RfDs for PFBS (CASRN 375-73-5) and the Related Compound K^+PFBS (CASRN 29420-49-3)

Endpoint/Reference	Species/Life Stage—Sex	Selected POD (HED)[a] (mg/kg-d)
		ov/bmd/session/10000 0084/"]
First estrous (litter *n*)[b]—[HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"]	Mouse/F_1—female	[HYPERLINK "https://hawcprd.epa.gov/bmd/session/10000 0025/"]

[a]Following [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=752972"] guidance, animal doses from candidate principal studies were converted to HEDs through the application of a DAF, where HED = dose × DAF. See [REF _Ref55818185 \h] in the assessment for full details. Links are to the HAWC BMDS session containing full modeling results for that endpoint.
[b]Fetal endpoints from [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"] were modeled alternatively using dose group sizes based either on total number of fetuses or dams. Given that it appears that [HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"] did not use the litter as the statistical unit of analysis, it is unclear if the study-reported standard errors pertain to litters or fetuses. Alternatively, modeling fetal endpoints using litter *n* or fetal *n* provides two modeling results that bracket the "true" variance among all fetuses in a dose group (i.e., using the fetal *n* will underestimate the true variance while using the litter *n* will overestimate the true variance). Individual animal data were requested from study authors but were unable to be obtained.

BMDL = benchmark dose lower confidence limit; BMDS = benchmark dose software; DAF = dosimetric adjustment factor; HAWC = Health Assessment Workspace Collaborative; HED = human equivalent dose; K^+PFBS = potassium perfluorobutane sulfonate; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; PFBS = perfluorobutane sulfonic acid; PND = postnatal day; POD = point of departure; RfD = oral reference dose; SD = standard deviation; T_4 = total thyroxine; TSH = thyroid-stimulating hormone.

study name	experiment name	animal description	endpoint name	observation time
Lieder, 2009, 1578546	90 Day Oral	Rat, Crl:Cd®(Sd)Igs Br Vaf/Plusim (♂)	Kidney, Hyperplasia, Papillary Tubular/Ductal Epithelium	90.0 days
		Rat, Crl:Cd®(Sd)Igs Br Vaf/Plusim (♀)	Kidney, Hyperplasia, Papillary Tubular/Ductal Epithelium	90.0 days
Lieder, 2009, 1578545	2 Generation Oral	F0 Rat, Sprague-Dawley (♂)	Kidney, Hyperplasia, Papillary Tubular/Ductal Epithelium	None not reported
		F0 Rat, Sprague-Dawley (♀)	Kidney, Hyperplasia, Papillary Tubular/Ductal Epithelium	None not reported
		F1 Rat, Sprague-Dawley (♂)	Kidney, Hyperplasia, Papillary Tubular/Ductal Epithelium	120.0 days
		F1 Rat, Sprague-Dawley (♀)	Kidney, Hyperplasia, Papillary Tubular/Ductal Epithelium	120.0 days
NTP, 2018, 4309741	28 Day Oral	Rat, Harlan Sprague-Dawley (♂)	Tetraiodothyronine (T4), Free	None not reported
		Rat, Harlan Sprague-Dawley (♀)	Tetraiodothyronine (T4), Free	None not reported
		Rat, Harlan Sprague-Dawley (♂)	Tetraiodothyronine (T4), Total	None not reported
		Rat, Harlan Sprague-Dawley (♀)	Tetraiodothyronine (T4), Total	None not reported
Feng 2017, 3856465	20 Day Oral Gestation	F0 Mouse, ICR (♀)	Tetraiodothyronine (T4), Free	20.0 gestational day (GD)
			Tetraiodothyronine (T4), Total	20.0 gestational day (GD)
		F1 Mouse, ICR (♀)	Tetraiodothyronine (T4), Total	1.0 post-natal day (PND)
				30.0 post-natal day (PND)
				60.0 post-natal day (PND)
			Tetraiodothyronine (T4), Total - Litter N	1.0 post-natal day (PND)
		F0 Mouse, ICR (♀)	Thyroid Stimulating Hormone (TSH)	20.0 gestational day (GD)
		F1 Mouse, ICR (♀)	Thyroid Stimulating Hormone (TSH)	1.0 post-natal day (PND)
				30.0 post-natal day (PND)
				60.0 post-natal day (PND)
			Eye Opening - Fetal N	12.0 post-natal day (PND)
			Eye Opening - Litter N	12.0 post-natal day (PND)
			First Estrous - Fetal N	24.0 post-natal day (PND)
			First Estrous - Litter N	24.0 post-natal day (PND)
			Vaginal Opening - Fetal N	24.0 post-natal day (PND)
			Vaginal Patency - Litter N	24.0 post-natal day (PND)

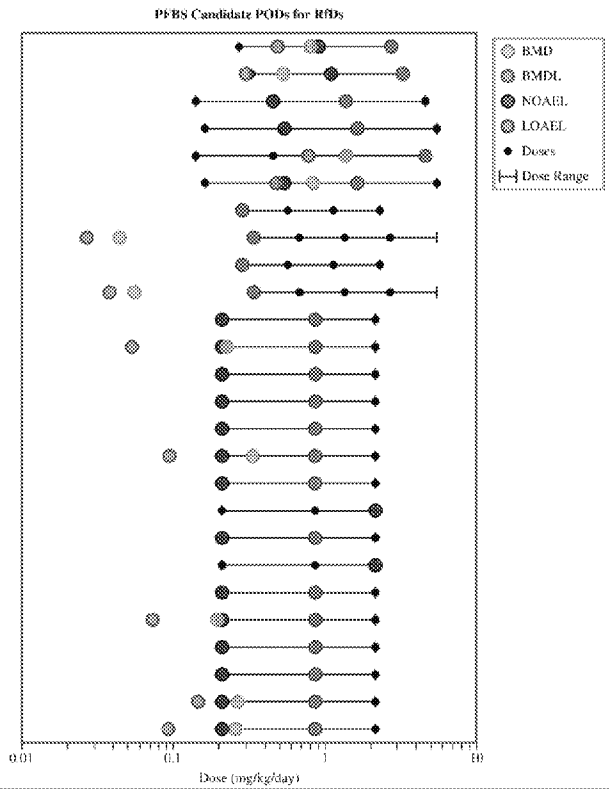

Figure F-[SEQ Figure_F- * ARABIC]. Candidate PODs for the Derivation of the Subchronic and Chronic RfDs for PFBS (Click to see [HYPERLINK "https://hawcprd.epa.gov/summary/data-pivot/assessment/100000037/pfbs-candidate-pods-subchronic-and-chronic-rfd/"])

F.2. MODELING PROCEDURE FOR CONTINUOUS NONCANCER DATA

BMD modeling of continuous data was conducted on the HAWC website using the U.S. Environmental Protection Agency's (U.S. EPA's) BMDS (Version 2.7). All continuous models available within the software were fit using a benchmark response (BMR) of 1 standard deviation (SD). For continuous data of effects in developing offspring, including thyroid hormone changes, a BMR of 0.5 SD change from the control mean is used to account for effects occurring in a sensitive life stage. A 1 SD BMR is also presented as the basis for model comparison as directed in the U.S. EPA *Benchmark Dose Technical Guidance* [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2012</Year><RecNum>1309</RecNum><IDText>1239433</IDText><DisplayText>(U.S. EPA, 2012)</DisplayText><record><rec-number>1309</rec-number><foreign-keys><key app="EN" db-id="ftttedd07r9pdbe29x4xrdxhw9rvdst2prtt" timestamp="1604957801">1309</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Benchmark dose technical guidance</title></titles><dates><year>2012</year></dates><pub-location>Washington, DC</pub-location><publisher>U.S. Environmental Protection Agency, Risk Assessment Forum</publisher><isbn>EPA/100/R-12/001</isbn><label>1239433</label><urls><related-urls><url>https://www.epa.gov/risk/benchmark-dose-technical-guidance</url></related-urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>]. An adequate fit is judged based on the χ^2 goodness-of-fit p-value ($p > 0.1$), magnitude of the scaled residuals in the vicinity of the BMR, and visual inspection of the model fit. In addition to these three criteria for judging adequacy of model fit, a determination is made as to whether the variance across dose groups is homogeneous. If a homogeneous variance model is deemed appropriate based on the statistical test provided by BMDS (i.e., Test 2), the final BMD results are estimated from a homogeneous variance model. If the test for homogeneity of variance is rejected ($p < 0.1$), the model is run again while modeling the variance 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. In cases in which a model with # parameters = # dose-groups was fit to the data set, all parameters were estimated, and no p-value was calculated, that model was not considered for estimating a POD unless no other model provided adequate fit. Among all models providing adequate fit, the BMDL from the model with the lowest Akaike's information criterion (AIC) was selected as a potential POD when BMDL values were sufficiently close (within threefold). Otherwise, the lowest BMDL was selected as a potential POD from which to derive the oral reference dose/inhalation reference concentration (RfD/RfC).

F.2.1 Modeling Predictions for Serum Total T_4 in PND 1 Female Offspring (litter *n*)

The modeling results for total T_4 in PND 1 female offspring (litter *n*) exposed Gestation Days (GDs) 1–20 are shown in [REF _Ref55818842 \h]. The Exponential 4 model (see [REF _Ref55819590 \h]) was selected given appropriate fit to the data and that the BMDL values differed by greater than threefold. The output for the U.S. EPA's BMDS model run is also provided below.

Table F-[SEQ Table_F- * ARABIC]. Modeling Results for Total T_4 in PND 1 Female Offspring (Litter *n*) Exposed GDs 1−20[a]

Model	Global *p*-Value	AIC	$BMD_{0.5SD}$ (HED) (mg/kg-d)	$BMDL_{0.5SD}$ (HED) (mg/kg-d)	BMD_{1SD} (HED) (mg/kg-d)	$BMDL_{1SD}$ (HED) (mg/kg-d)	Residual of Interest
Linear	0.5652	−4.74898	0.7778	0.5120	1.5557	1.0241	0.348
Polynomial	0.5652	−4.74898	0.7778	0.5120	1.5557	1.0241	0.348
Power	0.5652	−4.74898	0.7778	0.5120	1.5557	1.0241	0.348
Hill	−999	−1.89	0.368	0.0704	0.8677	0.2294	-6.01×10^{-7}
Exponential-M2	0.77	−5.3672	0.5546	0.3017	1.2555	0.6694	−0.5752
Exponential-M3	0.77	−5.3672	0.5546	0.3017	1.2555	0.6694	−0.5752
Exponential-M4[b]	**0.8583**	**−3.8581**	**0.3346**	**0.0951**	**0.8708**	**0.2498**	**−0.08305**
Exponential-M5	−999	−1.89	0.3807	0.0958	0.8669	0.2517	-4.356×10^{-7}

[a][HYPERLINK "https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=3856465"].
[b]Selected model. Exponential 4 model was selected given appropriate fit to the data and that the BMDL values differed by greater than threefold. The Hill and Exponential 5 models were not selected because they did not return a *p*-value.

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 0.5 SD = exposure concentration associated with 0.5 SD change from the control mean); BMR = benchmark response; GD = gestation day; HED = human equivalent dose; PND = postnatal day; SD = standard deviation; T_4 = thyroxine.

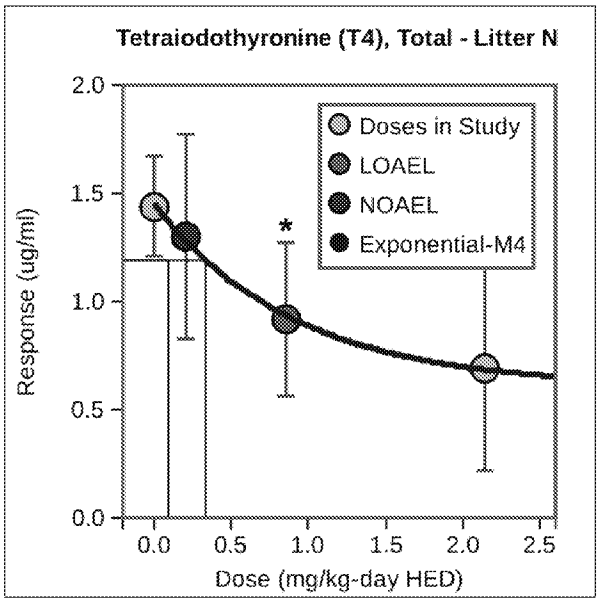

Figure F-[SEQ Figure_F- * ARABIC]. Exponential (Model 4) for Total T_4 in PND 1 Female Offspring (Litter *n*) Exposed GDs 1−20 [ADDIN EN.CITE <EndNote><Cite><Author>Feng</Author><Year>2017</Year><RecNum>1031</RecNum

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```
====================================================================
        Exponential Model.  (Version: 1.11;  Date: 03/14/2017)
        Input Data File: C:\Windows\TEMP\bmds-dfile-k4vsthrz.(d)
        Gnuplot Plotting File:
        Mon Aug 17 15:16:06 2020
 ====================================================================

 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.
```

```
Dependent variable = Response
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact


                Initial Parameter Values

                Variable          Model 4
                --------          --------
                  lnalpha          -1.29725
                      rho                 0 Specified
                        a             1.512
                        b           1.50054
                        c          0.434618
                        d                 1 Specified



                  Parameter Estimates

                 Variable          Model 4          Std.  Err.
                 --------          -------          ---------
                  lnalpha            -1.29645           0.0611565
                        a             1.45283            0.148029
                        b             1.10398             1.13864
                        c            0.417162            0.225239

  NC = No Convergence
```

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	1.44	0.329
0.21	10	1.3	0.657
0.86	10	0.92	0.493
2.14	10	0.69	0.657

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	1.453	0.523	-0.07759
0.21	1.278	0.523	0.1354
0.86	0.9337	0.523	-0.08305
2.14	0.6858	0.523	0.02529

Other models for which likelihoods are calculated:

```
Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

Model  R:        Yij = Mu + e(i)
           Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	5.944999	5	-1.889998
A2	8.698072	8	-1.396144
A3	5.944999	5	-1.889998

R	0.3138778	2	3.372244
4	5.929054	4	-3.858109

Additive constant for all log-likelihoods = -36.76. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	16.77	6	0.01017
Test 2	5.506	3	0.1383
Test 3	5.506	3	0.1383
Test 6a	0.03189	1	0.8583

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here.

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here.

The p-value for Test 6a is greater than .1. Model 4 seems to adequately describe the data.

```
  Benchmark Dose Computations:

    Specified Effect = 1.000000

            Risk Type = Estimated standard deviations from control

    Confidence Level = 0.950000

                 BMD =      0.87078

                BMDL =     0.249811

                BMDU =        21400


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         Gnuplot Plotting File:
                                                    Mon Aug 17 15:16:07 2020
=================================================================

BMDS_Model_Run
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  The form of the response function by Model:
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     Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

   Note: Y[dose] is the median response for exposure = dose;
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     Model 2 is nested within Models 3 and 4.
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A constant variance model is fit.

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Total number of records with missing values = 0
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Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact


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                Variable          Model 4          Std.  Err.
                --------          -------          ---------
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  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
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```

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           Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
           Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
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Additive constant for all log-likelihoods = -36.76. This constant added to the
above values gives the log-likelihood including the term that does not
depend on the model parameters.

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Test 2: Are Variances Homogeneous? (A2 vs. A1)
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Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
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levels, it seems appropriate to model the data.

The p-value for Test 2 is greater than .1. A homogeneous
variance model appears to be appropriate here.

The p-value for Test 3 is greater than .1. The modeled
variance appears to be appropriate here.

The p-value for Test 6a is greater than .1. Model 4 seems
to adequately describe the data.

Benchmark Dose Computations:

Specified Effect = 0.500000

```
        Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

             BMD =      0.33455

            BMDL =    0.0950923

            BMDU =      1.22544
```

F.3 MODELING PROCEDURE FOR DICHOTOMOUS NONCANCER DATA

BMD modeling of dichotomous noncancer data (see Figure F-1) was conducted on the HAWC website using the U.S. EPA's BMDS Version 2.7. For these data, the Gamma, Logistic, Log-Logistic, Log-Probit, Multistage, Probit, and Weibull dichotomous models available within the software were fit using a BMR of 10% extra risk. The Multistage model is run for all polynomial degrees up to $n - 2$, where n is the number of dose groups including control. Adequacy of model fit was judged based on the χ^2 goodness-of-fit p-value ($p > 0.1$), scaled residuals at the data point (except the control) closest to the predefined BMR (absolute value < 2.0), and visual inspection of the model fit. In the cases where no best model was found to fit to the data, use of a reduced data set without the high-dose group was further attempted for modeling and the result was presented along with that of the full data set. In cases in which a model with # parameters = # dose-groups was fit to the data set, all parameters were estimated, and no p-value was calculated, that model was not considered for estimating a POD *unless* no other model provided adequate fit. Among all models providing adequate fit, the BMDL from the model with the lowest AIC was selected as a potential POD when BMDL values were sufficiently close (within threefold) (see [REF _Ref55817942 \h]). Otherwise, the lowest BMDL was selected as a potential POD.

APPENDIX G. QUALITY ASSURANCE

U.S. EPA has an agency-wide quality assurance (QA) policy, and that policy is outlined in the *EPA Quality Manual for Environmental Programs* (see [HYPERLINK "https://www.epa.gov/irmpoli8/epa-quality-manual-environmental-program-requirements-implementing-quality-system"]) and follows the specifications outlined in U.S. EPA Order [HYPERLINK "https://www.epa.gov/sites/production/files/2013-10/documents/21050.pdf"]. The goal of the QA policy is to assure that environmental data used to support Agency decisions are of adequate quality and usability for their intended purpose.

As required by [HYPERLINK "https://www.epa.gov/sites/production/files/2013-10/documents/21050.pdf"], ORD maintains a Quality Management Program, which is documented in an internal Quality Management Plan (QMP). The latest version was developed in 2013 using the *Guidance for Developing Quality Systems for Environmental Programs (QA/G-1)*. An NCEA-specific QMP was also developed in 2013 as an appendix to the ORD QMP. Quality assurance for products developed within CPHEA is managed under the ORD QMP and applicable appendices.

This assessment has been designated as High Profile and is classified as QA Category A. Category A designations require reporting of all critical QA activities, including audits.

Another requirement of the Agency quality system includes the use of project-specific planning documents referred to as Quality Assurance Project Plans (QAPPs) that describe how specific data collection efforts will be planned, implemented, and assessed. Specific management of quality assurance in this assessment is documented in an Umbrella Quality Assurance Project Plan, which was developed using the U.S. EPA [HYPERLINK "https://www.epa.gov/quality/guidance-quality-assurance-project-plans-epa-qag-5"]. The latest approved version of the QAPP is dated September 2019. During assessment development, additional QAPPs may be applied for quality assurance management. They include:

Title	Document Number	Date
Program Quality Assurance Project Plan (PQAPP) for the Provisional Peer-Reviewed Toxicity Values (PPRTVs) and Related Assessments/Documents	L-CPAD-0032718-QP	October 2015 (last updated 2020)
Umbrella Quality Assurance Project Plan for NCEA PFAS Toxicity Assessments	B-IO-0031652-QP-1-2	July 2018 (last updated September 2019)
Quality Assurance Project Plan (QAPP) for Enhancements to Benchmark Dose Software (BMDS)	B-003742-QP-1-0	July 2019

During assessment development, this project underwent quality audit:

ED_006316_00006861-00358

Date	Type of Audit	Major Findings	Actions Taken
September 18, 2020	Technical System Audit	None	None

During assessment development, the assessment was subjected to external reviews by individual letters from expert peer reviewers and by other federal agency partners including the Executive Offices of the President. Peer-review reports during these review steps are available at [HYPERLINK "https://www.epa.gov/pfas/genx-and-pfbs-draft-toxicity-assessments"]. In addition, the assessment underwent public comment from November 21, 2018 to January 22, 2019. The public comments are available in the Docket ID No. EPA-HQ-OW-2018-0614. Prior to release, the final draft assessment was submitted to management and QA clearance. During this step the CPHEA QA director and QA managers review the project QA documentation and ensure U.S. EPA QA requirements have been met.

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APPENDIX H. REFERENCES

[ADDIN EN.REFLIST]

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