Perfluorodecanoic Acid (PFDA) and Salts

CAS Registry Numbers:
Perfluorodecanoic acid: 335-76-2
Ammonium perfluorodecanoate: 3108-42-7
Sodium perfluorodecanoate: 3830-45-3
Potassium perfluorodecanoate: 51604-85-4

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DSD History

Effective Date	Reason
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Acronyms and Abbreviations

Acronyms and Abbreviations	Definition
ACGIH	American Conference of Governmental Industrial Hygienists
AEGL	Acute Exposure Guideline Levels
AFFF	aqueous film forming foam
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
ATSDR	Agency for Toxic Substances and Disease Registry
$^{\circ}$C	degrees Celsius
CL	clearance
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMR	benchmark response
bw	body weight
CV	constant variance
DDEF	data-derived extrapolation factor
DSD	development support document
ESL	Effects Screening Level
^{acute}ESL	acute health-based Effects Screening Level for chemicals meeting minimum database requirements
$^{acute}ESL_{generic}$	acute health-based Effects Screening Level for chemicals not meeting minimum database requirements
$^{acute}ESL_{odor}$	acute odor-based Effects Screening Level
$^{acute}ESL_{veg}$	acute vegetation-based Effects Screening Level
$^{chronic}ESL_{threshold(c)}$	chronic health-based Effects Screening Level for threshold dose response cancer effect
$^{chronic}ESL_{threshold(nc)}$	chronic health-based Effects Screening Level for threshold dose response noncancer effects

Acronyms and Abbreviations	Definition
$^{chronic}ESL_{nonthreshold(c)}$	chronic health-based Effects Screening Level for nonthreshold dose response cancer effects
$^{chronic}ESL_{nonthreshold(nc)}$	chronic health-based Effects Screening Level for nonthreshold dose response noncancer effects
$^{chronic}ESL_{veg}$	chronic vegetation-based Effects Screening Level
F_{abs}	fraction absorbed
FSANZ	Food Standards Australia New Zealand
FXR	farnesoid X receptor
GD	gestation day
GLP	Good Laboratory Practices
GM	geometric mean
h	hour
HAWC	Health Assessment Workspace Collaborative
HED	human equivalent dose
HQ	hazard quotient
HSDB	Hazardous Substance Data Base
IARC	International Agency for Research on Cancer
IPCS	International Programme on Chemical Safety
IRIS	USEPA Integrated Risk Information System
kg	kilogram
KLH	keyhole limpet hemocyanin
K_{oc}	organic carbon-water partition coefficient
K_{ow}	n-octanol-water partition coefficient
LOAEL	lowest-observed-adverse-effect-level
LTD	limited toxicity data
mmHg	A millimeter of mercury; approximately 1 torr, or 1/760 of standard atmospheric pressure
µg	microgram
µg/m^3	micrograms per cubic meter of air

Acronyms and Abbreviations	Definition
mg	milligrams
mg/m^3	milligrams per cubic meter of air
min	minute
MOA	mode of action
MPS	mononuclear phagocyte system
MW	molecular weight
n	number
NHANES	National Health and Nutrition Examination Survey
NHMRC	Australian Government's National Health and Medical Research Council
NK	natural killer
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
NRC	National Research Council
$^{chronic}OAEL_{(nc)}$	chronic observed adverse effect level (noncancer effects)
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PBPK	physiologically based pharmacokinetic
PFAS	perfluoroalkyl and polyfluoroalkyl substances
PFC	perfluorinated compounds
PFDA	perfluorodecanoic acid
PFHxS	perfluorohexane sulfonic acid
PFOA	perfluorooctanoic acid
PFOS	perfluorooctane sulfonic acid
PFNA	perfluorononanoic acid
POD	point of departure
POD_{ADJ}	point of departure adjusted for exposure duration
POD_{HED}	point of departure adjusted for human equivalent dose

Acronyms and Abbreviations	Definition
POD_{int}	point of departure for internal dose
ppb	parts per billion
ppm	parts per million
PPARα	peroxisome proliferator activated receptor alpha
PXR	pregnane X receptor
ReV	reference value
Acute ReV	acute (e.g., 1-hour) health-based reference value for chemicals meeting minimum database requirements
Acute ReV-24hr	acute 24-hour health-based reference value for chemicals meeting minimum database requirements
Chronic $ReV_{threshold(nc)}$	chronic health-based reference value for threshold dose response noncancer effects
RfD	Reference dose
RPF	relative potency factor
SA	surface area
SD	Sprague-Dawley
SD	standard deviation
SFo	oral slope factor
SRBC	sheep red blood cells
TAMIS	Texas Air Monitoring Information System
TCEQ	Texas Commission on Environmental Quality
TD	Toxicology, Risk Assessment, and Research Division
ToBI	toxin binding inhibition
TRRP	Texas Risk Reduction Program
UF	uncertainty factor
UF_H	interindividual or intraspecies human uncertainty factor
UF_A	animal to human uncertainty factor
UF_{Sub}	subchronic to chronic exposure uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor

Acronyms and Abbreviations	Definition
UF_D	incomplete database uncertainty factor
URF	unit risk factor
USEPA	United States Environmental Protection Agency
V_E	minute volume
wk	week(s)
WOE	weight of evidence
yr	year(s)

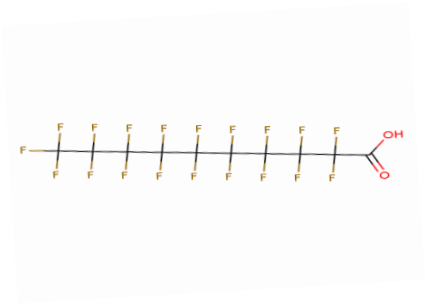
Chapter 1 Summary Tables

Table 1 and Appendix 4 provide summaries of health-based oral exposure values from a chronic evaluation of perfluorodecanonic acid (PFDA) and associated salts for use in TCEQ's remediation program (Texas Risk Reduction Program [TRRP]). Please refer to Section 1.1.2 of the *TCEQ Guidelines to Develop Toxicity Factors* (TCEQ 2015) for an explanation of how reference doses (RfDs) are used in the calculation of health-protective cleanup levels for the TCEQ's remediation program. Additionally, the tables in Appendix 4 provide observed adverse effect levels (OAELs) following oral exposure. These provide oral doses where health effects might be expected to occur in some people. Table 2 provides summary information and the physical/chemical data of PFDA and associated salts included in this development support document (DSD).

Table 1. Summary of Toxicity Factors for PFDA and Associated Salts

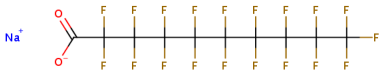
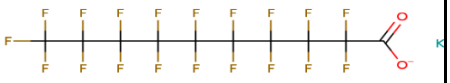
Toxicity Factor	PFDA	Ammonium perfluorodecanoate	Sodium perfluorodecanoate	Potassium perfluorodecanoate	Critical effect
Chronic oral RfD (mg/kg-d)	2.0E-07	2.1E-07	2.1E-07	2.1E-07	increased relative liver weight (female rats) in a 28-day oral study

Table 2. Chemical and Physical Data for Perfluorodecanoic Acid and Salts

Parameter	Perfluorodecanoic acid	Ammonium Perfluorodecanoate
Chemical Structure [a]		
Molecular Formula	$C_{10}HF_{19}O_2$	$C_{10}H_4F_{19}NO_2$
Molecular Weight	514.09 g/mol	531.12 g/mol
Physical State at 25°C	Solid	Solid
Color [b]	White	No data available
Odor	No data available	No data available
CAS Registry Number	335-76-2	3108-42-7
Common Synonym(s) [a]	PFDA; nonadecafluorodecanoic acid; perfluorocapric acid; nonadecafluorocapric acid; perfluoro-n-decanoic acid; nonadecafluoro-n-decanoic acid; 2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10 -nonadecafluorodecanoic acid	PFDAA; ammonium nonadecafluorodecanoate; decanoate, 2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10, 10,10-nonadecafluoro-, ammonium salt
Solubility in water [c]	4.2 mg/L	4.2 mg/L
Log K_{ow} [c]	2.34	2.34
Log K_{oc} [c]	3.17	3.17
Vapor Pressure [c]	2.5×10^{-7} mmHg	2.5×10^{-7} mmHg
Density [a]	1.79 g/cm^3 (experimental)	1.76 g/cm^3
Melting point [c]	167.01 °C	167.01 °C
Boiling point [c]	402.40 °C	402.40 °C

a: CompTox Chemicals Dashboard v2.4.1.
b: Color for perfluorodecanoic acid from PubChem.
c: Texas Risk Reduction Program (TRRP) table for sodium perfluorodecanoate.

Table 2. Chemical and Physical Data for Perfluorodecanoic Acid and Salts (cont'd)

Parameter	Sodium Perfluorodecanoate	Potassium Perfluorodecanoate
Chemical Structure [a]		
Molecular Formula	$C_{10}F_{19}NaO_2$	$C_{10}F_{19}KO_2$
Molecular Weight	536.07 g/mol	552.18 g/mol
Physical State at 25°C	Solid	Solid
Color	No data available	No data available
Odor	No data available	No data available
CAS Registry Number	3830-45-3	51604-85-4
Common Synonym(s) [a]	PFDA-Na; sodium nonadecafluorodecanoate; decanoic acid, 2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10, 10-nonadecafluoro-, sodium salt; nonadecafluorodecanoic acid sodium salt	2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10, 10-nonadecafluorodecanoic acid potassium salt; K-PFDA
Solubility in water [b]	4.2 mg/L	4.2 mg/L
Log K_{ow} [b]	2.34	2.34
Log K_{oc} [b]	3.17	3.17
Vapor Pressure [b]	2.5×10^{-7} mmHg	2.5×10^{-7} mmHg
Density [a]	1.76 g/cm^3	1.76 g/cm^3
Melting point [b]	167.01 °C	167.01 °C
Boiling point [b]	402.40 °C	402.40 °C

a: CompTox Chemicals Dashboard v2.4.1.
b: TRRP table for sodium perfluorodecanoate.

Chapter 2 Background Information

2.1 Physical/Chemical Properties

The perfluoroalkyl PFDA and associated salts exist as linear and branched isomers depending upon the method of production, and the reported values for the physical and chemical properties are typically reflective of the mixtures rather than a single specific isomer. Perfluoroalkyls are very stable due to the strength of the carbon-fluorine bonds, the presence of the three electron pairs surrounding each fluorine atom, and the shielding of the carbon atoms by the fluorine atoms. Therefore, as members of this chemical group, PFDA is not readily metabolized or degraded, and may accumulate in the human body and persist in the environment. Perfluoroalkyl carboxylates, such as PFDA, are resistant to direct photolysis and reaction with acids, bases, oxidants, and reductants. At environmentally and physiologically relevant pHs, PFDA and associated salts readily dissociate and will exist in the anion form (i.e., perfluorodecanoate) (ATSDR 2021).

Perfluoroalkyl carboxylates consist of a perfluorocarbon tail that is both hydrophobic and oleophobic and a charged end that is hydrophilic. This combination of hydrophobic and oleophobic characteristics makes these substances very useful as surfactants. The ability of these substances to repel oil, fat, and water has resulted in their use in surface protectants. Neutral or uncharged perfluoroalkyls or very long chain constituents are expected to form separate layers when mixed with hydrocarbons and water. Conversely, charged species, salts, and ionized species at relevant pH have relatively good solubility in water and alcohol. Both the potential to form separate layers when mixed with hydrocarbons and water and the propensity for charged or ionized perfluoroalkyls to concentrate at interfaces make the measurement of the n-octanol water partition coefficient impractical; therefore, values for log K_{ow} may be predicted values (ATSDR 2021).

2.2 Sources and Uses

Perfluoroalkyls, including PFDA and associated salts, are human-made organic compounds synthesized in a laboratory and do not occur naturally in the environment. These substances have been used extensively in surface coating and protectant formulations due to their unique surfactant properties. Major applications have included protectants for paper and cardboard packaging products, carpets, leather products, and textiles that enhance water, grease, and soil repellency, and in aqueous film forming foam (AFFF) used in firefighting. Perfluoroalkyls have also been used as processing aids in the manufacture of fluoropolymers such as nonstick coatings on cookware, membranes for clothing that are both waterproof and breathable, personal care products (such as dental floss, cosmetics, sunscreens), electrical wire casing, fire and chemical resistant tubing, and plumbing thread seal tape (ATSDR 2021).

PFDA has been detected in multiple environmental media including air, surface water, groundwater (including drinking water), soil, and food. The general population is exposed through food and water ingestion, dust ingestion, inhalation exposure, and hand-to-mouth transfer of materials containing these substances. PFDA has been detected in the serum of humans (https://www.cdc.gov/exposurereport/data_tables.html). In a study conducted from 1999 to 2018, the Centers for Disease Control and Prevention (CDC) found that 98% of Americans (sample size of approximately 1,500 to 2,200 individuals per sampling interval) have per- and polyfluoroalkyl substances (PFAS) in their serum. Generally, PFDA concentrations in blood have declined over time. PFDA has also been detected in human breast milk and umbilical cord blood (ATSDR 2021).

Chapter 3 Acute Evaluation

3.1 Health-Based Acute ReV and ^{acute}ESL and Health Based Acute 24-h ReV

A systematic review was conducted to identify inhalation toxicity studies to support development of acute inhalation toxicity factors for PFDA (Appendix 1). No human or animal studies examining inhalation effects following any duration of exposure (e.g., acute, short-term, gestational exposure) to PFDA have been identified. Furthermore, TCEQ has not identified a reliable physiologically-based pharmacokinetic (PBPK) model for PFDA that could be used for route-to-route extrapolation (i.e., oral to inhalation). This precludes the derivation of an acute reference value (ReV) and acute 24-h ReV.

3.2 Welfare-Based Acute Evaluation

3.2.1 Odor Perception

No odor data were found for PFDA and associated salts; therefore, an odor-based ESL was not assigned for these chemicals.

Chapter 4 Chronic Evaluation

A systematic review was conducted to identify inhalation and oral toxicity studies to support development of chronic inhalation toxicity factors and chronic oral toxicity factors for PFDA (Appendix 1). No human or animal studies examining inhalation effects following any duration of exposure (e.g., acute, subchronic, chronic, gestational exposure) to PFDA have been identified. Furthermore, TCEQ has not identified a reliable PBPK model for PFDA that could be used for route-to-route extrapolation (i.e., oral to inhalation). This precludes the derivation of a chronic ReV. Consequently, the following sections focus exclusively on the oral route of exposure.

4.1 Noncarcinogenic Potential

Per TCEQ guidelines (TCEQ 2015), when a toxicity factor (e.g., RfD) is identified in the scientific literature or databases, it is reviewed to determine whether the approaches used to develop the toxicity factor are sufficiently similar to those that the TCEQ would use for the given chemical dose-response assessment. TCEQ identified USEPA (2024) as a recent chemical dose-response assessment deriving an RfD for PFDA for consideration under TCEQ guidelines (TCEQ 2015). However, TCEQ identified several substantial scientific issues with the basis for USEPA's selected RfD (see Appendix 2) because the approaches that USEPA used to derive their selected RfD are different than those that TCEQ would utilize for the dose-response assessment of PFDA (e.g., leading to different conclusions regarding the quality and utility of certain epidemiological studies). Specifically, TCEQ concludes that the epidemiological studies are not suitable as a basis for dose-response assessment and RfD derivation for PFDA (although they have use for hazard identification), consistent with the governments of Australia and New Zealand (FSANZ 2021) and the U.S. Agency for Toxic Substances & Disease Registry (ATSDR 2021). Consequently, TCEQ did not adopt USEPA's RfD, consistent with relevant guidelines (TCEQ 2015). Instead TCEQ focused on toxicity study results in laboratory animals for the purposes of dose-response assessment and RfD derivation. Although TCEQ did not adopt the USEPA RfD, USEPA (2024) also evaluated a variety of endpoints in laboratory animals and derived human equivalent doses (HEDs) corresponding to various animal PODs (i.e., POD_{HED} values), which were useful for the current assessment. In the sections that follow, TCEQ reviews this and other information relevant to the dose-response assessment for PFDA to derive an RfD consistent with TCEQ guidelines, approaches, and scientific judgments.

4.1.1 Key and Supporting Studies

4.1.1.1 Human Studies

TCEQ identified significant scientific issues with the epidemiological studies that USEPA (2024, see Appendix 2) used as the basis for their selected RfD, leading to different conclusions regarding the quality and utility of these epidemiological studies. Specifically, the TCEQ concluded that epidemiological studies are not suitable as a basis for dose-response assessment and RfD derivation for PFDA. In short, these epidemiological studies involved exposures to mixtures of correlated PFAS, as well as other unquantified chemical exposures, and accurately ascertaining the contribution of an individual PFAS such as PFDA to the reported associated effects is not currently scientifically possible. TCEQ's conclusion is consistent with those of the governments of Australia and New Zealand (FSANZ 2021) and the U.S. ATSDR (ATSDR 2021). Consequently, this TCEQ assessment focuses on toxicity studies in laboratory animals for the purposes of PFDA dose-response assessment and RfD derivation. Further discussion of TCEQ's concerns about the PFAS epidemiology studies is provided in Appendix 2.

4.1.1.2 Animal Studies

This PFDA assessment focuses on toxicity study results in laboratory animals for the purposes of dose-response assessment and RfD derivation. The database for toxicity studies of PFDA in animals includes short-term oral studies in rodents and one oral prenatal developmental study in mice. No chronic toxicity studies of PFDA were available. Additionally, the database for PFDA lacks evaluations of postnatal development and a multigeneration reproductive toxicity study.

4.1.1.2.1 NTP (2022) 28-Day Oral Gavage Toxicity Study in Rats – Key Study

In this Good Laboratory Practices (GLP)-compliant study, PFDA formulated in 2% Tween 80 (polysorbate 80) in deionized water was administered via oral gavage to 10- to 11-week old Hsd:Sprague Dawley SD rats (Envigo, formerly Harlan Laboratories, Inc., Indianapolis, IN) at doses of 0 (vehicle control), 0.156, 0.312, 0.625, 1.25, or 2.5 mg/kg-d for 28 days. Each group comprised 10 males and 10 females. Animals were observed twice daily, and animals were weighed and clinical findings were recorded on the first day of dosing, weekly thereafter, and at the end of dosing. Vaginal samples were collected for 16 consecutive days prior to the end of dosing in the control, 0.625, 1.25, and 2.5 mg/kg-d groups and the percentage of time spent in the various estrous cycle stages and estrus cycle length were evaluated. Approximately 24 hours after administration of the last dose, all rats were anesthetized and blood was collected for hematology and clinical chemistry evaluations (including measurement of thyroid stimulating hormone, triiodothyronine, free thyroxine, and total thyroxine), measurement of testosterone concentrations, and measurement of PFDA in plasma. Additionally, blood samples from 5 rats/sex/group in all groups (except the 2.5 mg/kg-d group in which 3 samples were collected from males and no samples were collected from females) were collected for evaluation of micronuclei in reticulocytes. Animals were necropsied and the following organs were weighed: right adrenal gland, heart, right kidney, liver, lungs, spleen, right testis, thymus, thyroid gland, and uterus/cervix/vagina. A complete histopathologic evaluation was performed on all rats in the control and 2.5 mg/kg-d groups. Gross lesions, kidney, liver, pancreas, stomach (males only), bone marrow, spleen, thymus, nose, ovary, testes, and thyroid gland were examined in the 0.156, 0.312, 0.625, and 1.25 mg/kg-d groups. Additionally, the epididymis was examined in the 0.625 and 1.25 mg/kg-d groups. Sperm samples were collected from the control and 0.625, 1.25 and 2.5 mg/kg-d groups and the following parameters were evaluated: spermatid heads per testis and per gram testis, spermatid counts, and epididymal motility and concentration; the left cauda, left epididymis and left testis were also weighed. It is noted that the duration of dosing in this study (4 weeks) is less than the time needed to make a full assessment of the effect on spermatogenesis in rats (which occurs over a period of approximately 10 weeks [Creasy 2001]). Liver samples were collected from males for measurement of PFDA concentrations and determination of acyl-coenzyme A (CoA) oxidase activity. Liver samples were collected from males and females for gene expression of Acox1 and cytochrome P450 enzymes (Cyp4a1, Cyp2b1, and Cyp2b2).

Concentrations of PFDA were detected in plasma of male controls (at least 386-fold lower than lowest dose) and of female controls (at least 218-fold lower than lowest dose). With the exception of the 2.5 mg/kg-d dose, at the same administered dose, mean plasma concentrations in females were marginally higher (≤30%) compared to those in males. At 2.5 mg/kg-d, mean plasma concentrations were similar in males and females. Plasma concentrations of PFDA increased in a greater than dose-proportional manner in males and females, and liver concentrations of PFDA in males increased in a slightly lower than dose proportional manner with an increase in dose. Increased hepatic acyl-CoA activity was seen at all doses of PFDA. Gene expression of Acox1, Cyp4a1, Cyp2b1, and Cyp2b2 were increased in liver samples collected from males and females at all doses of PFDA. The increased gene expression of Acox1 and Cyp4a1 is consistent with activation of the peroxisome proliferator-activated receptor alpha (PPARα) and increased expression of Cyp2b1 and Cyp2b2 indicated activation via the constitutive androstane receptor (CAR).

All rats survived to the end of dosing and no clinical observations related to PFDA were observed. Overall body weight gain was decreased in males and females administered 1.25 mg/kg-d. Over the course of dosing, males and females in the 2.5 mg/kg-d group lost weight. In the 2.5 mg/kg-d group, body weight losses (using the mean body weight values) from Days 1 to 29 in males and females were 22% and 25%, respectively. When compared to the control group at the end of dosing in the 1.25 and 2.5 mg/kg-d groups, mean body weights in males were 21% and 38% lower, respectively, and mean body weights in females were 12% and 36% lower, respectively. Males and females in the 1.25 and 2.5 mg/kg-d groups had decreased reticulocyte counts, along with decreased mean cell volume. Increased mean cell hemoglobin concentration was seen in males administered ≥ 0.625 mg/kg-d and in females administered 2.5 mg/kg-d. Increased erythrocytes were seen in males in the 2.5 mg/kg-d group. Increased erythrocytic parameters (erythrocytes, hematocrit, hemoglobin) were observed in females in the 1.25 and 2.5 mg/kg-d groups. Platelets were decreased in females in the 2.5 mg/kg-d group. Increased urea nitrogen was seen in males and females in the 1.25 and 2.5 mg/kg-d groups. The increases in urea nitrogen and erythrocytic parameters may have been due to decreased water intake, as rats in the 1.25 and 2.5 mg/kg-d groups had decreased body weight gain and body weight loss, respectively. Decreased food consumption and concomitant decreased water intake likely led to the body weight deficits in these dose groups, resulting in increased urea nitrogen and hemoconcentration.

Decreased glucose was observed in males and females in the 1.25 and 2.5 mg/kg-d groups, and decreased creatinine was seen in males in the 1.25 mg/kg-d group and in males and females in the 1.25 and 2.5 mg/kg-d groups; the authors state that these decreases were likely due to decreased food consumption and body weight decrements. In males, cholesterol was decreased only in the 0.156, 0.312, and 0.625 mg/kg-d groups and triglycerides were decreased in the 1.25 and 2.5 mg/kg-d groups. In females, cholesterol was decreased in the 2.5 mg/kg-d

group only. In males, total protein and globulin were decreased at all doses of PFDA, albumin was decreased at ≥ 1.25 mg/kg-d, and albumin/globulin ratio was increased at all doses of PFDA. In females, albumin was increased at 0.312 and 0.625 mg/kg-d, globulin was decreased at ≥ 0.312 mg/kg-d and albumin/globulin ratio was increased at all doses of PFDA.

In males, alanine aminotransferase (ALT) was increased by 1.4-fold in the 0.312 and 0.625 mg/kg-groups, aspartate aminotransferase (AST) was increased up to 1.4-fold at all doses of PFDA, and alkaline phosphatase (ALP) increased at ≥ 0.312 mg/kg-d. In females, ALT was increased up to 1.4-fold and AST was increased up to 1.8-fold in the 1.25 and 2.5 mg/kg-d groups, and ALP was increased at ≥ 0.625 mg/kg-d. In males and females, bilirubin (total, indirect, and direct) and bile acids were increased in the 1.25 and 2.5 mg/kg-d groups. In females, sorbitol dehydrogenase was increased at 2.5 mg/kg-d and creatine kinase was increased at 1.25 and 2.5 mg/kg-d. In males, free thyroxine was decreased at ≥ 0.312 mg/kg-d, and total thyroxine was decreased only in the 0.312 mg/kg-d group. In females, triiodothyronine was increased and free thyroxine was decreased in the 1.25 and 2.5 mg/kg-d groups.

At all doses of PFDA in males and females, absolute and relative liver weights were increased. Compared to controls, the magnitude of increase in absolute liver weights was 14-23% in males and 17-32% in females, and the magnitude of increase in relative liver weights was 11-91% in males and 12-102% in females. Relative kidney weights were increased in males and females administered ≥ 0.625 mg/kg-d. Relative thyroid weights were increased in males in the 1.25 and 2.5 mg/kg-d groups, and absolute and/or relative thyroid weights were increased in females at ≥ 0.312 mg/kg-d. Absolute and relative thymus and spleen weights were decreased in males and females in the 1.25 and 2.5 mg/kg-d groups.

Right and left testis weights were decreased in males in the 2.5 mg/kg-d group. Left cauda epididymis and left epididymis weights were decreased at doses of 1.25 and 2.5 mg/kg-d, and sperm counts were decreased in the 2.5 mg/kg-d group. Male serum testosterone concentrations were 64% and 75% lower than control in the 1.25 and 2.5 mg/kg-d groups, respectively. Histopathologic findings in the testes were minimal or mild interstitial cell atrophy in the 1.25 and 2.5 mg/kg-d groups, minimal to moderate spermatid retention in the seminiferous tubules, and minimal or marked degeneration of the germinal epithelium. In the epididymis, histopathologic findings were minimal to marked exfoliated germ cells in the ducts.

Females administered ≥ 0.625 mg/kg-d were evaluated for reproductive toxicity. None of the rats in the 2.5 mg/kg-d group were cycling, and extended diestrus was observed in the 1.25 and 2.5 mg/kg-d groups. Females administered ≥ 0.312 mg/kg-d had higher serum testosterone concentrations (32%, 74%, 145%, and 355% higher than controls in the 0.312, 0.625, 1.25, and 2.5 mg/kg-d groups, respectively).

Cytoplasmic alteration of hepatocytes was observed in males and females administered ≥ 0.625 mg/kg-d. Statistically significant increases in hepatocyte hypertrophy in males and females in the 1.25 and 2.5 mg/kg-d groups, cytoplasmic vacuolization of hepatocytes in males in the 1.25 mg/kg-d group and in males and females in the 2.5 mg/kg-d group, and hepatocyte necrosis in females in the 2.5 mg/kg-d group were observed. The severity of the hepatocellular lesions generally increased with an increase in dose.

Bone marrow hypocellularity (minimal to moderate) was confined to the 2.5 mg/kg-d group and was observed in all males and females. In the thymus, minimal or mild lymphocyte apoptosis was observed in males in the 1.25 mg/kg-d group, and minimal to moderate atrophy was seen in males and females in the 2.5 mg/kg-d group. The bone marrow hypocellularity and thymic atrophy observed in the 2.5 mg/kg-d group likely were due to the severe body weight loss, as a result of inappetence (https://ntp.niehs.nih.gov/atlas/nnl/hematopoietic-system/bone-marrow/Hypocellularity) (https://ntp.niehs.nih.gov/atlas/nnl/immune-system/thymus/Atrophy).

The peripheral blood micronucleus test was negative in males and females; findings consistent with bone marrow toxicity (decreased reticulocytes at 1.25 and 2.5 mg/kg-d) were observed.

In summary, the target organs of toxicity were the liver (increased absolute and relative weights; histopathologic findings; increased serum levels of ALT, AST, ALP, sorbitol dehydrogenase; decreased globulin and albumin; increased bilirubin and total bile acids), male reproductive tract (decreased testis and epididymis weights; decreased sperm count; decreased serum testosterone; histopathologic findings in the testis and epididymis), female reproductive tract (alterations in estrous cyclicity, increased serum testosterone), and thymus (apoptosis of lymphocytes). Bone marrow hypocellularity and thymic atrophy observed in the 2.5 mg/kg-d group are likely related to inappetence and resultant body weight loss over the course of dosing. The body weight loss observed in the 2.5 mg/kg-d group also may have contributed to the lack of estrous cycling in this group.

A no-observed-adverse-effect-level (NOAEL) was not identified in this study. The lowest-observed-adverse-effect-level (LOAEL) for oral administration of PFDA for 28 days was the low-dose of 0.156 mg/kg-d in which increased absolute (14-17%) and relative (11-12%) liver weights were observed in males and females.

4.1.1.2.2 Frawley et al. (2018) 28-Day Oral Gavage Study in Female Rats and Mice

PFDA formulated in 2% Tween 80 in deionized water was administered via oral gavage to 7- to 9-week old specific pathogen-free female Harlan Sprague Dawley rats (Envigo, Indianapolis, IN) at doses of 0 (vehicle control), 0.125, 0.25, 0.5, 1, or 2 mg/kg-d for 28 days. Formulated PFDA also was administered via oral gavage to 8- to 10-week old pathogen-free female B6C3F1/N mice (Taconic Biosciences, Inc., Germantown, NY) at doses of 0, 0.3125, 0.625, 1.25, 2.5 or 5

mg/kg once per week for 4 weeks (Days 1, 8, 15 and 22). The authors stated that the rationale for once weekly dosing in mice was based on species-specific differences in toxicokinetics between rats and mice. The study comprised 11 separate cohorts of rats (8/group) and 11 separate cohorts of mice (8/group) for the evaluation of toxicity and immunotoxicity endpoints. Animals were weighed prior to initiation of dosing and on Days 1, 8, 15, 22, and 29. On Day 29 animals were euthanized, and the following organs were weighed: liver, spleen, lungs, thymus, and kidneys. Blood was collected for evaluation of hematology parameters. In rats only, the following tissues were processed for histopathologic examination: liver, spleen, lungs, thymus, kidneys, adrenal glands, bone marrow (femur), gastrointestinal tract with Peyer's patches, and lymph nodes (mesenteric, submandibular, and popliteal). The following immunotoxicity assays also were performed in this study: (1) single cell suspensions of spleen were prepared for flow cytometry for enumeration of various white cell populations, (2) a spleen IgM antibody-forming cell response to sheep red blood cells (SRBC) was performed using a modified hemolytic plaque assay, (3) serum IgM antibody titers to SRBC or keyhole limpet hemocyanin (KLH) in rats were evaluated, (4) a mixed-leukocyte response assay to DBA/2 mouse spleen cells was performed in mice, (5) T-cell proliferation following stimulation with anti-CD3+ antibody was evaluated, (6) a delayed type hypersensitivity response to *Candida albicans* was performed, (7) natural killer (NK) cell activity was assessed, (8) in vivo activity of the mononuclear phagocyte system (MPS) was evaluated following intravenous injection of SRBC in rats, (9) ex vivo femoral bone marrow DNA synthesis, colony formation, and differentials were performed, and (10) host resistance to intranasally administered influenza virus (*Influenza A*/Hong Kong/8/68 [H3N2]) was performed in mice. A positive control group was included for each of the immunotoxicity assays, and the positive controls worked as expected in each assay.

Rat study

In rats administered 1 mg/kg-d, decreased body weight gain was observed; on Day 29 mean body weight and body weight gain were 5% and 21% lower than control, respectively. At the 2 mg/kg-d dose, 2 out of 88 rats exhibited body weight loss of > 20% in 5 days and were euthanized. Rats administered 2 mg/kg-d initially had decreased body weight gain followed by body weight loss. On Day 29 in the 2 mg/kg-d group, the mean body weight and body weight gain were 22% and 103% lower than control, respectively. Due to the adverse clinical observations, and in accordance with NTP Laboratory Animal Management guidelines (NTP 2011), rats in the 1 and 2 mg/kg-d groups were excluded from further evaluation. Therefore, further evaluations were conducted in rats in the 0, 0.125, 0.25, and 0.5 mg/kg-d groups.

Organ weights were evaluated in 3 cohorts (histopathology, MPS immunotoxicity, and T-cell response to SRBC). Increases in absolute and relative liver weights were seen in all 3 cohorts. When compared to controls, absolute liver weights were increased at 0.25 and 0.5 mg/kg-d and relative liver weights were increased at all doses. The magnitude of increase in absolute and

relative liver weights were 10-39% and 8-35%, respectively. In one cohort each, absolute and relative thymus weights were increased in the 0.125 and 0.25 mg/kg-d groups only, and relative kidney weights were increased at ≥ 0.25 mg/kg-d while absolute kidney weight was increased at 0.5 mg/kg-d. There were no histopathologic correlates for the differences in thymus and kidney weights.

The only statistically significant findings in hematology parameters were a minimal decrease in mean corpuscular hemoglobin (~7%) at 0.25 mg/kg-d and minimal decreases in mean corpuscular hemoglobin concentration (5-6%) at 0.25 and 0.5 mg/kg-d. Histopathologic findings were seen in the liver only. In 3 out of 8 rats in the 0.5 mg/kg-d group, minimal centrilobular, single cell hepatocyte necrosis was observed. No effects on the total spleen cell numbers or on absolute or relative values of splenic B cells, T cells, T cell subsets, NK cells, or macrophages were seen. Administration of PFDA to rats did not affect the antibody forming response to SRBC (3 assays performed), or the serum IgM antibody levels to SRBC or KLH. PFDA had no effect in two assays of cell-mediated immunity (T cell proliferative response to anti-CD3+ stimulation, delayed type hypersensitivity to *Candida albicans*). In two assays, the total numbers of spleen cells were decreased by 15-23% at 0.25 mg/kg-d and/or 0.5 mg/kg-d relative to control. PFDA administration had no effect in the NK cell assay, an assessment of innate immunity. In a different assessment on innate immunity, phagocytosis of tissue macrophages in the liver and thymus was altered, although the vascular half-life of ^{51}Cr-labeled SRBC was not different from control. In the liver, there was a trend at the 0.25 and 0.5 mg/kg-d dose for decreased uptake by tissue macrophages, whereas in the thymus at 0.5 mg/kg-d there was an increased uptake by tissue macrophages. PFDA had no effect on DNA synthesis in the ex vivo bone marrow assay; at 0.25 mg/kg-d only, there was an increase in the percentage of CD11b/c+ cells (granulocyte/monocyte) cells but there were no differences in absolute numbers of subsets of cells.

In summary, in rats administered PFDA orally daily for 28 days, administration of 0.125, 0.25 and 0.5 mg/kg-d resulted in an increase in relative liver weights. A NOAEL was not identified in this study, and the LOAEL was 0.125 mg/kg-d based on increased relative liver weight observed in the MPS immunotoxicity assay (10%).

Mouse study

On Day 29, mean body weight and body weight gain in mice in the 5 mg/kg group were 2.9% and 22% lower than control. Organ weights were evaluated in 1 cohort. At ≥ 0.625 mg/kg absolute and relative liver weights were increased by 26-89% and 16-81%, respectively. Relative spleen weights were decreased at ≥ 1.25 mg/kg and absolute spleen weight was decreased at 5 mg/kg. There were no hematology findings in mice. In mice in the 5 mg/kg group total spleen cell numbers were decreased by 24% due to decreases in absolute numbers of B cells, T cells, helper T cells, cytotoxic T cells, NK cells, and macrophages. However, at 5 mg/kg the

percentages of these cell types did not differ from control. Administration of PFDA to mice did not affect the antibody forming response to SRBC. PFDA had no effect in three assays of cell-mediated immunity (T cell proliferative response to anti-CD3+ stimulation, delayed type hypersensitivity to *Candida albicans*, mixed leukocyte response assay). In one assay, the total spleen cell number at the 5 mg/kg dose was decreased by 24% relative to control. PFDA administration had no effect in the NK cell assay, an assessment of innate immunity. The ex vivo bone marrow DNA synthesis assay was performed three times; in one assay at 0.625 mg/kg only, there was a decrease in the total cells/femur. Host resistance to *Influenza* virus was evaluated at 3 different dilutions (corresponding to 0%, 25%, and 42% moribundity in the vehicle control group). When compared to the respective vehicle control group, PFDA administration had no effect on survival of mice at any dose or at any of the three virus challenge levels.

The NOAEL in the mouse study was 0.3125 mg/kg PFDA administered orally once/wk for 4 wk. The LOAEL was 0.625 mg/kg PFDA administered orally once/wk for 4 wk due to increased absolute (26%) and relative (16%) liver weights.

4.1.1.3 Reproductive and Developmental Studies

One oral prenatal developmental study in mice was conducted with PFDA. The database for PFDA lacks evaluations of postnatal development and a multigeneration reproductive toxicity study. Although the study duration was not of sufficient duration for evaluation of an entire spermatogenic cycle in rats, reproductive organs (testes, epididymis, and ovaries) were examined microscopically and other reproductive endpoints were evaluated in males and females in the 28-day oral gavage study in rats (NTP 2022, see Section 4.1.1.2.1).

4.1.1.3.1 Harris and Birnbaum (1989) Prenatal Developmental Toxicity Study in Mice

PFDA was evaluated in a prenatal developmental toxicity study in which pregnant mice were dosed during gestation day (GD) 10-13 or GD 6-15. The authors state that dosing performed on GD 10-13 corresponded to the window of sensitivity for development of cleft palate and hydronephrosis, while dosing during GD 6-15 covered the entire period of organogenesis. Female C57BL/6N mice (Charles River Laboratories, Raleigh, NC) were acclimated for at least 2 weeks prior to mating with males from a breeding colony. Mated females were 8-10 weeks old. Groups of pregnant females (10-14/group) were dosed with PFDA formulated in corn oil via oral gavage on GD 10-13 at doses of 0 (vehicle control), 0.25, 0.5, 1, 2, 4, 8, 16, or 32 mg/kg-d or on GD 6-15 at doses of 0, 0.03, 0.1, 0.3, 1, 3, 6.4, or 12.8 mg/kg-d. Mice were checked daily for signs of toxicity and were weighed on the first dose day and on GD 18. On GD 18 the dams were terminated and maternal liver weights, live fetus weights, and numbers of live and dead fetuses were recorded. Maternal body weight gain was defined as the gain in weight of the dam between the first day of dosing and GD 18 minus the weight of the uterus and contents. The fetuses were examined grossly and then approximately half were preserved for evaluation of

soft tissue and the other half were preserved for skeletal evaluations. In the study where dams were dosed on GD 10-13, fetuses were examined for external malformations and cleft palate in all dose groups, and for hydronephrotic kidneys in the control and high-dose (32 mg/kg-d) groups only; no evaluations for skeletal abnormalities were performed. In the study where dams were dosed on GD 6-15, fetuses were examined for external malformations, cleft palate, and skeletal defects in all dose groups, and for visceral malformations or variations in the control and high-dose (12.8 mg/kg-d) groups only.

Dosing of dams on GD 10-13

All dams survived. Maternal body weight gain was statistically significantly decreased at 16 mg/kg-d and statistically significantly increased at 32 mg/kg-d. Maternal absolute and relative liver weights were increased at ≥ 1 mg/kg-d. Mean maternal absolute and relative liver weights were 11-68% and 12-106% higher than control, respectively. No statistically significant differences were seen in numbers of implantations per litter, percent resorptions per litter, and percentage of litter with resorption. Although not statistically significant, the number of live fetuses per litter and litters with 100% resorptions was higher in the 32 mg/kg-d group compared to control. Mean fetal body weights were decreased at ≥ 0.5 mg/kg-d. In the fetuses evaluated, no cleft palate or hydronephrosis was observed.

In summary, in dams dosed on GD 10-13, due to increased maternal absolute and relative liver weights, the NOAEL and LOAEL for maternal toxicity were 1 and 2 mg/kg-d, respectively. Based on decreased mean fetal body weights, the NOAEL and LOAEL for fetal toxicity were 0.25 and 0.5 mg/kg-d, respectively.

Dosing of dams on GD 6-15

Doses ≥ 6.4 mg/kg-d were maternally toxic. Over the course of gestation, dams in the 6.4 mg/kg-d group had decreased body weight gain and dams in the 12.8 mg/kg-d group lost body weight. Three dams in the 12.8 mg/kg-d dose group died on GD 18. Concomitant with maternal toxicity in the 6.4 and 12.8 mg/kg-d groups, the numbers of live fetuses were statistically significantly lower in comparison to control. Although not statistically significant, the number of resorptions per litter and number of litters with complete resorptions were higher in the 12.8 mg/kg-d group when compared to control. There were no differences in number of implantations per litter. Maternal absolute and relative liver weights were increased at ≥ 1 mg/kg-d. Mean maternal absolute and relative liver weights were 22-67% and 18-127% higher than control, respectively. Mean fetal body weights were decreased at ≥ 3 mg/kg-d. In the fetuses evaluated, no hydronephrosis, cleft palate or soft tissue malformations were seen. No skeletal malformations were seen; however, all fetuses in the 12.8 mg/kg-d group had skeletal variations (delay in braincase ossification). Also, in the 6.4 and 12.8 mg/kg-d groups,

other skeletal variations (absence of fifth sternebrae, delay in ossification of phalanges) were increased relative to control.

In summary, in dams dosed on GD 6-15, due to increased maternal absolute and relative liver weights, the NOAEL and LOAEL for maternal toxicity were 1 and 3 mg/kg-d, respectively. Based on decreased mean fetal body weights, the NOAEL and LOAEL for fetal toxicity were 1 and 3 mg/kg-d, respectively.

4.1.2 Selection of the Key Study and Critical Effect

In regard to the focus on animal studies, USEPA (2024) evaluates a variety of endpoints in laboratory animals and derives POD_{HED} values corresponding to animal PODs for a variety of endpoints, which we considered in our analysis. Table 5-10 of USEPA (2024) provides candidate POD_{HED} values for RfD derivation based on various liver effects (increased serum AST, ALP; increased relative liver weight), reproductive effects (cauda epididymis sperm count, Leydig cell atrophy, testosterone, testis weight, cauda and whole epididymis weights, uterus weight, numbers of days in estrus/diestrus), and developmental effects (decreased fetal body weight) observed in the 28-day rat studies of NTP (2022) and Frawley et al. (2018) and/or the developmental toxicity mouse study of Harris and Birnbaum (1989). See USEPA (2024) and Section 4.1.1.2 for additional details on, and discussion of, these candidate key animal studies (NTP 2022, Frawley et al. 2018, Harris and Birnbaum 1989). Note that in Frawley et al. (2018), liver weights were collected in 3 separate assays in female SD rats. The text in Section 4.1.1.2.2 describes the overall findings from all assays, and the LOAEL for increased liver weight was observed in the MPS immunotoxicity assay. USEPA (2024) separated out the liver weight results for each assay and that benchmark dose modeling was performed for results of two assays (histopathology cohort, MPS immunotoxicity cohort) and a NOAEL/LOAEL approach was used for increased liver weights observed in the third assay (T cell dependent antibody response). Because all these endpoints represent potential critical effects for RfD derivation, the POD_{HED} values corresponding to both the benchmark dose (BMD)/LOAEL values ($POD_{HED\text{-}BMD/LOAEL}$) and BMDL/NOAEL values ($POD_{HED\text{-}BMDL/NOAEL}$) are provided in Table 3; these values were obtained from Table 5-10 in USEPA (2024), except for the decreased fetal body weight on GD 10-13 that came from Birnbaum and Harris (1989). TCEQ then calculated the $POD_{HED\text{-}BMD/LOAEL}$ values for these endpoints because the agency evaluates critical effect(s) based on LOAEL-/BMD-type values (TCEQ 2015).

Data were extracted and reviewed for other laboratory animal studies as well. However, they were not included in Table 3 because they were not candidate key studies for RfD derivation, because their $POD_{HED\text{-}BMD/LOAEL}$ values would have been appreciably higher by comparison. As brief examples, the studies of Takagi et al. (1991) and Zhou et al. (2017) provide LOAELs of 15.5 mg/kg-d (dose calculated by TCEQ) and 25 mg/kg-d, respectively, for effects such as increased relative liver and kidney weights in rats, and disorganized alignment of epithelial cells and

increased inflammatory cell infiltration in the mouse stomach. However, these PODs are 12- to 167-fold higher than the LOAEL/BMD-based values provided in Table 3, which includes candidate critical effects in both species. Similarly, while Wang et al. (2020) identifies a LOAEL of 8 mg/kg-d (dose calculated by TCEQ) for body weight loss and increased mortality in mice, this POD is 16 times higher than that for decreased fetal body weight effects based on the mouse study in Harris and Birnbaum (1989). These appreciable differences in the LOAEL/BMD-type values utilized under TCEQ (2015) to determine critical effects are why additional animal studies were not considered as candidate key studies for RfD derivation (though data were extracted and initially considered by TCEQ), and so are not included in Table 3.

Table 3. Candidate Key Studies, Adverse Effects, Points of Departure and Human Equivalent Oral Doses for RfD Derivation

Study	Duration	Effect	Strain species, sex	NOAEL/BMDL POD basis [a]	POD [a] (mg/kg-d)	$POD_{HED\text{-}NOAEL/BMDL}$ (mg/kg-d) [a]	Derived adjustment factor [b]	LOAEL/BMD POD basis [c]	POD [c] (mg/kg-d)	$POD_{HED\text{-}LOAEL/BMD}$ (mg/kg-d) [d]
NTP (2022)	28 days	Increased AST	SD rat, male	BMDL 1SD, Hill CV	0.123	4.93E-04	2.49E+02	BMD 1SD, Hill CV	0.327	1.31E-03
		Increased AST	SD rat, female	NOAEL (1% increase)	0.625	3.70E-03	1.69E+02	LOAEL (31% increase)	1.25	7.40E-03
		Increased ALP	SD rat, male	NOAEL (9% increase)	0.156	6.25E-04	2.50E+02	LOAEL (22% increase)	0.312	1.25E-03
		Increased ALP	SD rat, female	NOAEL (14% increase)	0.156	8.24E-04	1.89E+02	LOAEL (34% increase)	0.312	1.65E-03
		Increased relative liver weight	SD rat, male	BMDL 10RD, Hill CV	0.170	7.21E-04	2.36E+02	BMD 10RD, Hill CV	0.208	8.81E-04
		Increased relative liver weight	SD rat, female	BMDL 10RD, Hill CV [e]	0.112	5.92E-04	1.89E+02	BMD 10RD, Hill CV	0.154	8.16E-04
		Decreased days in estrus	SD rat, female	BMDL 5RD, linear CV	0.128	6.76E-04	1.89E+02	BMD 5RD, linear CV	0.150	7.90E-04
Frawley et al. (2018)	28 days	Increased relative liver weight	SD rat, female (histopathology study cohort)	BMDL 10RD, Exp 2 CV	0.222	1.27E-03	1.75E+02	BMD 10RD, Exp2 CV	0.293	1.68E-03
		Increased relative liver weight	SD rat, female (MPS study cohort)	BMDL 10RD, linear CV	0.187	1.04E-03	1.80E+02	BMD 10RD, linear CV	0.242	1.35E-03

Study	Duration	Effect	Strain species, sex	NOAEL/BMDL POD basis [a]	POD [a] (mg/kg-d)	$POD_{HED\text{-}NOAEL/BMDL}$ (mg/kg-d) [a]	Derived adjustment factor [b]	LOAEL/BMD POD basis [c]	POD [c] (mg/kg-d)	$POD_{HED\text{-}LOAEL/BMD}$ (mg/kg-d) [d]
		Increased relative liver weight	SD rat, female (TDAR study cohort)	NOAEL (2% increase)	0.125	6.61E-04	1.89E+02	LOAEL (19% increase)	0.250	1.32E-03
Harris and Birnbaum (1989)	GD 6-15	Decreased fetal body weight	C57BL/6N mice, male and female	NOAEL (4% decrease)	1	6.68E-02	1.50 E+01	LOAEL (6% decrease)	3	2.00E-01
	GD 10-13	Decreased fetal body weight	C57BL/6N mice, male and female	NOAEL (4% decrease) [f]	0.25	1.67E-02	1.50E+01	LOAEL (10% decrease)	0.5	3.34E-02

Abbreviations: BMD, benchmark dose; BMDL, benchmark dose lower confidence limit; CV, constant variance; GD, gestation day; LOAEL, lowest-adverse-effect-level; MPS, mononuclear phagocyte system; NOAEL, no-observed-adverse-effect-level; POD, point of departure; RD, relative deviation; SD, standard deviation; SD rat, Sprague Dawley rat; TDAR, T cell dependent antibody response

a: See Table 5-10 of USEPA (2024).

b: Derived toxicokinetic adjustment factor calculated as the respective POD divided by the POD_{HED} for the cited effect. See Section 4.1.4.3 Default Dosimetry Adjustments from Animal-to-Human Exposure for details regarding dosimetric adjustments based on toxicokinetic dose adjustment factors.

c: Based on BMD results from Appendix C.2 of USEPA (2024) or the LOAEL determined by TCEQ from the cited study.

d: Calculated as the POD for the cited effect divided by the derived toxicokinetic adjustment factor.

e: Highest dose dropped for adequate model fit to the data.

f: Included by TCEQ as an additional POD for the cited effect for comparison.

As stated above, TCEQ evaluates critical effect(s) based on LOAEL or BMD values (TCEQ 2015), so $POD_{HED\text{-}BMD/LOAEL}$ values are the primary focus in selection of the critical effect. Increased relative liver weight and decreased number of days in estrus (both in female SD rats) based on NTP (2022) provide the lowest $POD_{HED\text{-}BMD/LOAEL}$ values in Table 3. The $POD_{HED\text{-}BMD}$ values are very similar and both round to 8E-04 mg/kg-d at one significant figure. This value is reasonably similar to (i.e., within 1.6-fold of) the lower end of the $POD_{HED\text{-}BMD/LOAEL}$ range for serum liver enzyme (AST and ALP) effects based on NTP (2022) (1.25E-03 to 7.40E-03 mg/kg-d). Consequently, an RfD based on increased relative liver weight and decreased number of days in estrus as co-critical effects, would also be expected to be health protective of these individual serum liver enzyme effects. An RfD based on these critical effects would also be expected to be health-protective of male reproductive effects and other female reproductive effects as these effects are less sensitive and have higher POD_{HED} values (see Table 5-10 of USEPA 2024). Ultimately, the $POD_{HED\text{-}BMDL/NOAEL}$ values that would be used for RfD derivation for these less sensitive reproductive effects range from 1.12E-03 mg/kg-d (increased number of days in diestrus) to 6.25E-03 mg/kg-d (decreased absolute testis weight), compared to the lower $POD_{HED\text{-}BMDL}$ values of 5.92E-04 and 6.76E-04 mg/kg-d for RfD derivation based on increased relative liver weight and decreased days in estrus (both in female rats in NTP 2018), respectively. Such an RfD would also be protective for the decreased fetal body weight observed in Harris and Birnbaum (1989), which is associated with the appreciably higher $POD_{HED\text{-}LOAEL}$ and $POD_{HED\text{-}NOAEL}$ values of 3.34E-02 and 1.67E-02 mg/kg-d, respectively.

Consistent with the discussion above, NTP (2022) has been identified as the key study. The co-critical effects identified are increased relative liver weight and decreased number of days in estrus, both in female rats of the NTP (2022) study. These effects have the lowest $POD_{HED\text{-}BMD/LOAEL}$ values of the candidate critical effects identified based on laboratory animal toxicity studies. In regard to RfD calculations for these co-critical effects, the $POD_{HED\text{-}BMDL}$ values are 5.92E-04 and 6.76E-04 mg/kg-d, respectively, for increased relative liver weight and decreased days in estrus, in female SD rats of NTP (2022). These values will be used for RfD derivation.

4.1.3 MOA Analysis and Dose Metric

Decreased Number of Days in Estrus

Information on the potential PFDA modes of action (MOAs) affecting days in estrus is extremely limited. In the NTP (2022) 28-day gavage study in rats, Wyeth-14,643 (a peroxisome proliferator activated receptor alpha [PPARα] agonist) was shown to cause effects on estrous cyclicity, notably extended diestrus, which also was seen in rats administered PFDA. However, mechanistic studies that investigate the role of PPARα in PFDA-altered estrous cyclicity are not available. The MOA by which PFDA affected days in estrus in the key study (NTP 2022) is unknown.

Increased Relative Liver Weight

TCEQ generally concurs with USEPA (2024) that overall, the available evidence from in vivo studies is that PFDA exposure can result in organ-level effects such as increases in liver weights that may be observed across multiple species and may be mediated, at least in part, by PPARα-independent mechanisms (see Appendix D of USEPA 2024).

As discussed in Section 3.2.1 of USEPA (2024), overall, the mechanistic evidence supports the biological plausibility of liver effects observed in animal bioassays. Further, the available data indicate a likely role for both PPARα-dependent and -independent mechanisms in the hepatotoxicity of PFDA in animals. Existing evidence from in vitro studies and animal models considered more relevant to humans with respect to PPARα sensitivity suggest that some responses may be conserved across species (including activation of relevant nuclear receptor pathways (PPARα/γ, pregnane X receptor [PXR], and farnesoid X receptor [FXR]) and outcomes related to hepatocellular stress, mitochondrial damage, lipid accumulation, and liver enlargement). Taken together, these data provide some support for the potential human relevance of the observed hepatic effects in animals, although uncertainties remain (e.g., limited in vivo information to characterize the putative involvement of PPARα and other cell signaling pathways in the mechanisms of hepatotoxicity of PFDA in animals and humans).

Regarding information on structurally related long-chain PFAS, USEPA (2024) indicates that collectively, studies in PPARα null and humanized animal models for structurally related long-chain PFAS are consistent with a plausible PPARα-dependent and -independent MOA for PFDA liver toxicity, adding further support to the potential human relevance of the observed liver effects in laboratory animals. The PPARα-dependent MOA alone is not relevant to humans as the key events that occur following PPARα activation are not observed in primary human hepatocytes and in non-human primates following exposure to PPARα agonists (Corton et al. 2014). Additionally, the evidence suggests that these PFAS have the potential to induce steatosis.

Lastly, USEPA (2024) evaluates the data for PFDA within the context of Hall et al. (2012). Hall et al. indicated that concordant histopathological evidence of degenerative or necrotic changes (e.g., hepatocyte necrosis, fibrosis, inflammation, steatosis, biliary degeneration, and necrosis of resident cells within the liver) can be used to support the argument that liver weight/ hepatocyte enlargement are adverse. USEPA concludes that overall, the available evidence for PFDA meets all the Hall et al. (2012) criteria for adversity and supports the conclusion that PFDA exposure has multiple and coherent effects on liver histopathology, serum biomarkers, and liver weights in exposed animals (primarily rats) that support the findings of adverse liver effects in animals. For example, in addition to increased relative liver weight and hepatocyte hypertrophy, PFDA caused cytoplasmic alterations and vacuolization as well as necrosis in rat hepatocytes in 28-day gavage studies (Frawley et al. 2018, NTP 2022). In the 28-day studies in

SD rats, minimal single cell necrosis of hepatocytes (Frawley 2018) and minimal necrosis of foci of hepatocytes with mononuclear inflammatory cells (NTP 2022) were seen and are consistent with hepatocellular injury. The hepatic lesions showed a clear pattern of increased incidence and severity with an increase in dose (NTP 2022). Consistent with these observations, steatosis, necrosis, edema, and degeneration were reported in CD-1 mice offered PFDA in drinking water for 12 days (Wang et al. 2020). Moreover, increases in serum alanine aminotransferase (ALT, up to 1.4-fold higher than control) and serum AST (up to 1.8-fold higher than control) were seen in SD rats in the 28-day gavage study. In the 12-day study in CD-1 mice, serum ALT and AST values were approximately 4.4- and 7.5-fold higher than controls, respectively. In the 28-day gavage study in rats (NTP 2022), alterations in other serum biomarkers were observed and included increases in ALP, bilirubin (total, direct, and indirect), and total bile acids, which are indicators of hepatobiliary function; and decreases in total protein, globulin and/or albumin with concomitant increases in albumin/globulin ratio. In summary, the hepatic effects seen in rodents were consistent with liver hypertrophy and injury and meet the Hall et al. (2012) criteria for adversity. Steatosis is a common liver response in animals associated with exposure to PFAS (e.g., PFOA, PFHxS, PFNA) (USEPA 2024).

In conclusion, as discussed in USEPA (2024), while the activation of PPARα in the MOA for noncancer liver effects in rodents may not be relevant to human health assessment, PFDA also interacts with other nuclear receptors and cell signaling pathways relevant to its potential mechanism of hepatotoxicity in both human and animal models. Furthermore, some hepatic effects observed in animals occurred at least in part independent of PPARα or were found to be activated in human in vitro assays or animal models that are more relevant to humans with respect to PPARα sensitivity. These observations are consistent with studies in PPARα null and humanized animals for other long-chain PFAS (e.g., perfluorooctanoic acid [PFOA], perfluorohexane sulfonic acid [PFHxS], perfluorononanoic acid [PFNA]) that suggest non-PPARα mechanisms of liver toxicity. Given that the precise role of PPARα in the noncancer liver effects of PFDA remains largely unknown and the possible involvement of PPARα-dependent and -independent pathways, the effects observed in animals are considered potentially relevant to humans. TCEQ generally agrees that the available mechanistic information overall provides support for the biological plausibility of the phenotypic liver effects observed in exposed animals as well as the activation of relevant molecular and cellular pathways across human and animal models in support of the human relevance of the animal findings. See Section 3.2.1 and Appendices D and E of USEPA (2024) for a more detailed discussion of data and findings relevant to potential MOAs for the liver effects observed in laboratory animals.

4.1.4 Adjustments to the POD

4.1.4.1 BMD Modeling

The BMD modeling results in Table 3 of Section 4.1.1.2 were obtained from USEPA (2024), either Table 5-10 (BMDLs) or Appendix C (BMDs in addition to BMDLs). See USEPA (2024) for additional information.

4.1.4.2 Default Exposure Duration Adjustments

The oral doses utilized are expressed as average mg/kg-d, so no further exposure duration adjustments are necessary, as is standard practice in regulatory dose-response assessments conducted by TCEQ and USEPA. However, it should be noted that the animal studies relevant for derivation of a RfD were subchronic in duration, for which a subchronic-to-chronic uncertainty factor (UF_{Sub}) is later applied to adjust POD_{HED} values for the co-critical effects (see Section 4.1.5 Adjustments to the POD_{HED}).

4.1.4.3 Default Dosimetry Adjustments from Animal-to-Human Exposure

The approach for pharmacokinetic (PK) extrapolation of PFDA between rodent animal models (i.e., rats, mice) and humans is discussed in Section 3.1.7 of USEPA (2024). Briefly, as stated in that section, while USEPA's classical PK model underpredicted the observed plasma concentrations of PFDA in rats at the end of the NTP 28-day bioassay, the agency considered the qualitative model behavior (i.e., the shape of the predicted time-course over the 28 days of exposure) to be a reasonably accurate prediction. More specifically, model predictions in Figure G-8 of USEPA (2024) show an essentially linear increase in serum PFDA over the course of the study, which is consistent with the mean estimated half-lives of 83 and 61 days in male and female rats, respectively (see Table 3-3 of USEPA 2024). If the actual time-course is similar to the predicted time-course, then the average serum concentration over the course of a 28-day bioassay, which USEPA considered to be a reasonable measure of internal dose for use in animal-to-human extrapolation, will simply be one-half the final plasma concentration. Hence, USEPA concluded that assuming this relationship while using the measured end-of-study PFDA plasma concentrations would provide a more accurate prediction of the average concentration than calculating the average using the PK model. For rat PODs that are between the doses used in the NTP bioassay (i.e., those obtained from BMD modeling or from other studies in SD rats), the presumed end-of-study plasma concentration was then obtained by USEPA by linear interpolation between the mean observed concentrations. Given the fairly linear relationship between exposure and the end-of-study plasma concentrations in the NTP bioassay, shown as data points representing mean ±SD in Figure G-9 of USEPA (2024) and reproduced below, such interpolation was expected to be reasonably accurate. Note that because the internal dose (or POD_{int}) varies with dose and sex (as shown in Figure G-9) and is used in interspecies extrapolation (from rats-to-humans) per the calculation of POD_{HED} shown below, different rat

PODs in Table 3 (e.g., BMDs, BMDLs, NOAELs, and LOAELs) have different interspecies adjustment factors (e.g., female rats in Frawley et al. 2018). Note that (NTP 2018) shown in the reproduced Figure G-9 from USEPA (2024) is the previous version of the key study (NTP 2022); no changes in plasma concentrations of PFDA were noted in the revised report (NTP 2022).

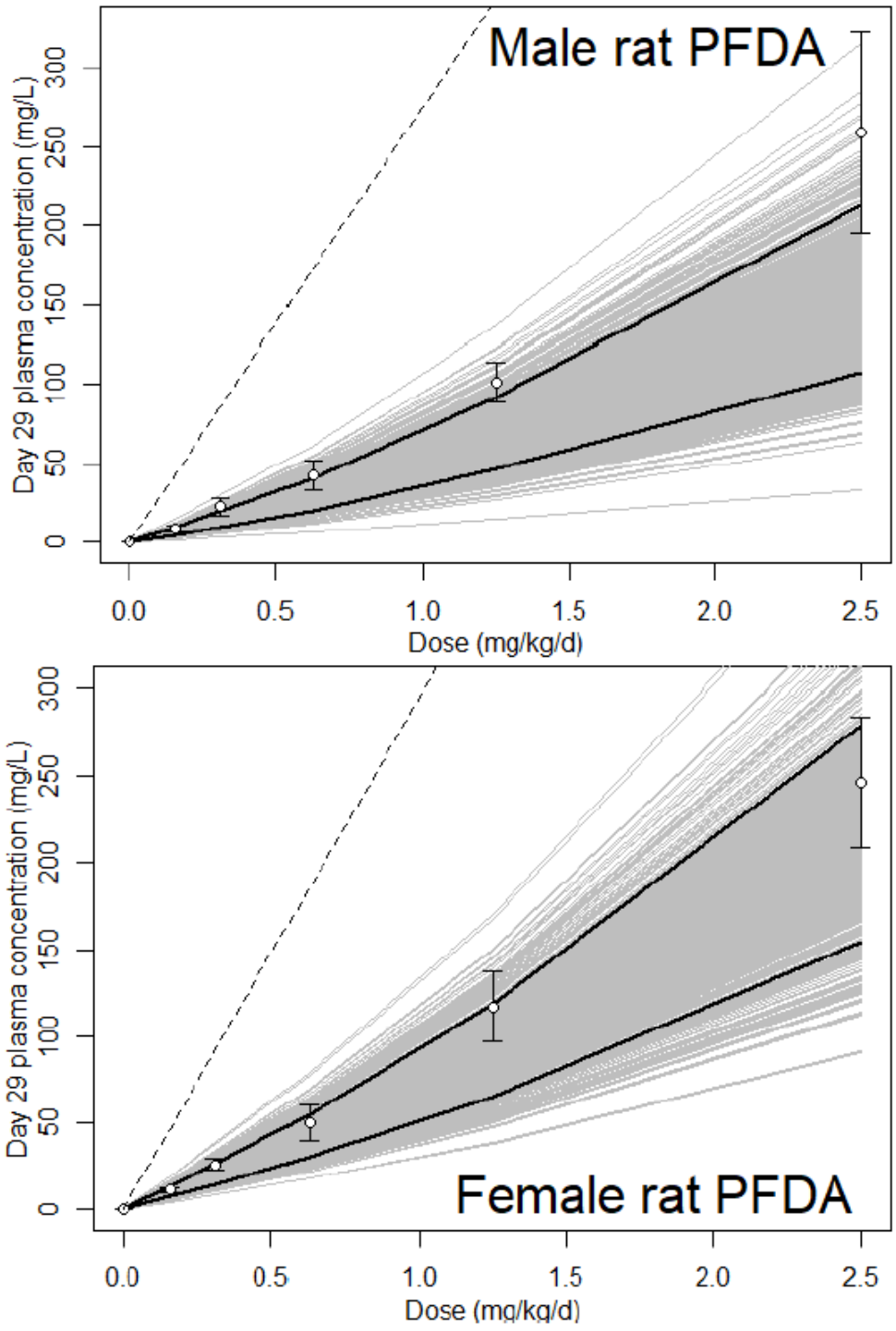


Figure G-9. Measured end-of-study of PFDA in male and female rats in the NTP bioassay (NTP, 2018) as a function of dose versus model predictions. Points are mean ± SD serum concentrations measured at the end of the bioassay (NTP, 2018). Gray lines are results from the PK model using 1,000 posterior parameter samples from the Bayesian analysis (see Appendix G.1). Solid black lines are 5th and 95th percentiles of the samples. Dashed line is the steady-state serum concentration, i.e., dose/clearance.

As with modeled or interpolated rat plasma internal POD (POD_{int}) values, when USEPA (2024) obtained a plasma concentration directly from rat toxicity studies, USEPA calculated the POD_{HED} as:

$$POD_{HED} = POD_{int} \times CL_H$$

where the clearance in humans, CL_H = 0.147 mL/kg-d = 1.47×10^{-4} L/kg-d (see Table 3-3 of USEPA 2024).

This is the exposure rate for which the steady-state human serum concentration will equal the rat POD_{int}.

In contrast to the NTP 28-day study in rats, in-study PK data were not available for the mouse developmental study of Harris and Birnbaum (1989), making both evaluation of PK model predictions and interpolation of observed serum concentrations impossible. As stated in USEPA's guidance for data-derived extrapolation factors (DDEFs, USEPA 2014), use of these factors "maximize the use of available data and improve the scientific support for a risk assessment." As discussed above in Section 3.1.4 of USEPA (2024), the estimated population average values of CL for mice and humans are considered sufficiently sound for use in such extrapolation and use of the alternative (default) approach, $BW^{3/4}$ scaling, would lead to significant errors in HED calculations. Therefore, a DDEF calculated from the CL values for female mice and humans listed in Table 3-3 of USEPA (2024) is considered the next preferred option for extrapolation to humans from developmental endpoints observed in mice (the CL for female mice is used specifically since exposure to the mouse fetus occurs through dosing to the dam and it is the dam's CL that determines the internal dose). As described in Appendix G.2.3 of USEPA (2024), the POD_{HED} can be calculated from the F_{abs} and CL in the animal and humans as:

$$POD_{HED} = POD_A \times (F_{abs,A}/F_{abs,H}) \times CL_H/CL_A$$

where $F_{abs,H}$ and CL_H are the fraction absorbed and clearance in humans, while $F_{abs,A}$ and CL_A are the fraction absorbed and clearance in the animal.

The DDEF is then $(F_{abs,A}/F_{abs,H}) \times CL_H/CL_A$. As discussed in Section 3.1.1 of USEPA (2024), F_{abs} was estimated to be 100% in mice while $F_{abs,H}$ is assumed to be 100%. With CL = 2.2 mL/kg-d in female mice and 0.147 mL/kg-d in humans (see Table 3-3 of USEPA 2024), the DDEF for female mouse to human extrapolation is 0.067.

TCEQ finds these approaches to be reasonable. The POD_{HED} values in Table 3 reflect these animal-to-human PK adjustments.

4.1.5 Adjustments to the POD_{HED}

For the co-critical effects of increased relative liver weight and decreased number of days in estrus, in female SD rats of NTP (2022), the $POD_{HED\text{-}BMDL}$ values are 5.92E-04 and 6.76E-04 mg/kg-d, respectively, will be used for candidate RfD derivation. The following uncertainty factors (UFs) were applied to these POD_{HED} values:

- A total UF_H of 10 is based on the default $UF_{H\text{-}TD}$ of 3 (or 3.16 as the square root of 10) for potential toxicodynamic intrahuman variability multiplied by a $UF_{H\text{-}TK}$ of 3 (or 3.16 as the square root of 10) for toxicokinetic intrahuman variability. The default $UF_{H\text{-}TK}$ of 3 appears sufficiently conservative given a toxicokinetic intrahuman variability factor of 2.7 based on differences in clearance measured among different human population groups from Zhang et al. (2013) (see Table 2 of that study). Accordingly, TCEQ considers a factor of 3 (or 3.16 as the square root of 10) to account for toxicokinetic intrahuman variability to represent a reasonable value for use in conjunction with a $POD_{HED\text{-}BMDL}$ based on sensitive co-critical effects (i.e., increased relative liver weight, decreased number of days in estrus) in laboratory animals. The calculations to generate the alternative toxicokinetic factor of 2.7 are described below, as well as the reasons for choosing the default factor of 3 for toxicokinetic variability.
    - 0.096 mL/d-kg arithmetic mean clearance for older males and females as the less sensitive group (higher clearance) ÷ 0.035 mL/d-kg arithmetic mean 95% lower bound clearance for young females as the more sensitive group (lower clearance) = 2.7. Values derived using other possible clearance rates generated even smaller levels of variance between human populations. For example, using clearance for the arithmetic mean clearance for older males and females (higher clearance) ÷ the arithmetic mean for younger females as the more sensitive group (lower clearance) results in a factor of only 1.4 (i.e., 0.096 mL/d-kg ÷ 0.066 ml/d-kg = 1.4, see Table 2 of Zhang et al. 2013).
- A UF_A of 3 is applied to primarily account for uncertainty in potential toxicodynamic differences between rats and humans. Aspects of the cross-species extrapolation of toxicokinetic processes have been accounted for by using a PK approach that interpolated measured PFDA plasma concentrations in rats from the NTP 28-d bioassay and a PFDA clearance estimated from human data. While reasonable animal-to-human PK extrapolation approaches were utilized by USEPA (2024) and adopted by TCEQ, some residual PK uncertainty remains as does the primary uncertainty considered here, potential interspecies toxicodynamic differences. Given these considerations, the application of a UF_A of 3 is both justified and reasonable.
- A UF_L of 1, because $POD_{HED\text{-}BMDL}$ values are considered NOAELs.

- A UF_{Sub} of 10 is applied for subchronic to chronic extrapolation for the increased relative liver weight and decreased number of days in estrus because of the subchronic exposure duration and the presumption that effects might occur at lower doses and/or be more severe with longer (i.e., chronic) exposures. As stated by USEPA (2024): (1) PFDA-induced effects on estrous cyclicity were observed to be of large magnitude in the 28-day study, and it is possible that PFDA-induced effects on estrous cyclicity could become more sensitive or lead to more severe downstream effects like infertility with longer exposure durations; and (2) for liver effects, increases in relative liver weights demonstrated a time dependency across short-term exposures,[a] and the limited data for liver weight suggest the potential for increased sensitivity with increasing duration, although there is no information on how liver weight or other sensitive liver endpoints (increased AST and ALP levels) are impacted by increases in exposure duration past 28 days for PFDA. Consistent with the above discussion, a full UF_{Sub} value of 10 is justified. It should further be noted that the UF_D value selected (10) also considers the lack of longer-term (i.e., chronic) exposure studies for which the UF_{Sub} (10) is applied. Consequently, the total UF associated with database uncertainty, including the lack of chronic oral exposure animal studies, may be viewed to be at least 100 (i.e., UF_{Sub} of 10 × UF_D value of 10 = 100).
- A UF_D of 10 is applied to account for deficiencies and uncertainties in the laboratory animal database. The limited evidence base in laboratory animals consists of short-term studies in two rodent species and a medium to high confidence prenatal developmental study in mice. As discussed previously, while multiple epidemiological studies for PFDA appear in the literature and are useful as part of the weight of evidence (WOE) for hazard identification, such studies were deemed unsuitable for dose-response assessment and toxicity factor (i.e., RfD) derivation by TCEQ (see Appendix 2), ATSDR (2021), and the Australian and New Zealand governments (FSANZ 2021). Significant uncertainties exist regarding the lack of studies examining the effects of long-term (i.e., chronic) PFDA exposure in laboratory animals, including studies of potential multigenerational effects. Chronic animal studies or reliable epidemiological studies might reveal more sensitive/severe effects or adverse effects at lower oral doses. Consistent with appreciable database concerns (i.e., low database quality) and Table 5-2 of TCEQ (2015), TCEQ selects a UF_D value of 10. Furthermore, it should be noted that other UFs are also related to the UF_D. For example, the selected UF_{Sub} value of 10 is only necessary due to a deficiency of chronic toxicity studies in

[a] Relative liver weight increased by 17%-56% at 1.15-10 mg/kg-d in rats exposed for 7-14 days and by 12%-127% at 1-16 mg/kg-d in mice exposed during gestion (GD 10-13 and 6-15). Similar magnitudes of liver weight increases were achieved in rodents after 28-day exposure, but at lower PFDA doses (10%-102% at 0.125-2.5 mg/kg-d in rats and 16%-81% at 0.089-0.71 mg/kg-d in mice). (USEPA 2024)

the database. Consequently, the total UF associated with database uncertainty may be viewed to be at least 100 (i.e., UF_D value of 10 × UF_{Sub} of 10 = 100).

Accordingly, the total combined UF is 3,000, although perhaps a lower UF_D value might be considered appropriate considering the database as a whole for structurally similar PFAS (i.e., other perfluorinated carboxylates). Regardless, the final total combined UF selected by TCEQ for RfD derivation is 3,000, the maximum under TCEQ guidelines (see Section 3.12 of TCEQ 2015).

candidate RfD for increased relative liver weight:
= POD_{HED} / (UF_H x UF_A x UF_L x UF_{SUB} x UF_D)
= 5.92E-04 mg/kg-d / (10 x 3 x 1 x 10 x 10)
= 5.92E-04 mg/kg-d / 3,000
= 1.97E-07 mg/kg-d or 2.0E-07 mg/kg-d (rounded to two significant figures)

candidate RfD for decreased number of days in estrus:
= POD_{HED} / (UF_H x UF_A x UF_L x UF_{SUB} x UF_D)
= 6.76E-04 mg/kg-d / (10 x 3 x 1 x 10 x 10)
= 6.76E-04 mg/kg-d / 3,000
= 2.25E-07mg/kg-d or 2.2E-07 mg/kg-d (rounded to two significant figures)

These candidate RfD values are very similar, with the higher value being only 1.1 times the lower value. While either value would be protective of both co-critical effects, TCEQ conservatively selects the slightly lower candidate RfD value of or 2.0E-07 mg/kg-d based on increased relative liver weight observed in female SD rats of the NTP (2022) study as the final RfD for PFDA.

Final RfD = 2.0E-07 mg/kg-d (based on increased relative liver weight)

4.1.6 Health-Based Chronic RfD

In deriving the chronic RfD, no numbers were rounded between equations until the RfD was calculated. The chronic RfD was rounded to two significant figures (Table 4).

Table 4. Derivation of the Chronic RfD for PFDA and Associated Salts

Parameter	Summary
Study	NTP (2022)
Study Population	SD rats
Study Quality	High

Parameter	Summary
Exposure Method	Oral gavage
Critical Effects	Increased relative liver weight (female rats)
Exposure Duration	28 days
LOAEL/BMD	0.154 mg/kg-d (BMD_{10})
NOAEL/BMDL	0.112 mg/kg-d ($BMDL_{10}$)
POD_{HED}	5.92E-04 mg/kg-d ($BMDL_{10\text{-}HED}$)
Total UFs	3,000 (maximum default)
Interspecies UF	3
Intraspecies UF	10
LOAEL UF	1 (or N/A)
Subchronic to chronic UF	10
Incomplete Database UF *Database Quality*	10 low
Chronic RfD	**2.0E-07 mg/kg-d**

a: When adjusted for differences in molecular weight, the RfD is 2.1E-07 mg/kg-d for ammonium perfluorodecanoate, sodium perfluorodecanoate, and potassium perfluorodecanoate.

4.1.7 Chronic Noncarcinogenic OAEL

Risk managers, and the general public, often ask to have information on the doses where health effects would be expected to occur. So, when possible, the TCEQ provides chemical-specific observed adverse effects levels in DSDs (TCEQ 2015). As the basis for development of observed-adverse-effect-levels (OAELs) is limited to available data, future studies could possibly identify a lower POD for this purpose. The chronic noncarcinogenic OAEL is provided for informational purposes only (TCEQ 2015).

The lowest $LOAEL_{HED\ oral}$ was 7.90E-04 mg/kg-d (see Table 3) which was identified in NTP (2022) for decreased number of days in estrus in SD rats. This was followed closely by increased relative liver weight as the critical effect ultimately utilized for the RfD ($LOAEL_{HED\ oral}$ of 8.16E-04 mg/kg-d; Table 3). Therefore, the OAEL for PFDA is 7.90E-04 mg/kg-d. The margin of exposure (MOE) between the OAEL of 7.90E-04 mg/kg-d and the RfD is 3,950 times for PFDA.

4.2 Carcinogenic Potential

4.2.1 Carcinogenic Weight of Evidence

TCEQ concurs with recent conclusions by USEPA (2024) that, considering the limitations in the evidence base across human, animal, and mechanistic studies of PFDA (see Section 3.3 of USEPA 2024) and in accordance with the USEPA Guidelines for Carcinogen Risk Assessment (USEPA 2005), the evidence is *inadequate to assess carcinogenic potential* of PFDA in humans. Briefly, (1) the available epidemiologic evidence on PFDA and the risks of cancer is limited and generally uninformative (p. 3-288 of USEPA 2024); (2) there are no long-term animal bioassay studies available for PFDA (p. 3-289 of USEPA 2024); and (3) PFDA does not appear to elicit a strong genotoxic response as demonstrated by the lack of activity in most assays described in USEPA (2024), including mutagenicity tests in prokaryotic organisms and mammalian cells, sister chromatid exchange and cell transformation assays in vitro, and unscheduled DNA synthesis, oxidative DNA damage and micronucleus assays in rats (p. 3-291 of USEPA 2024). This limited evidence amounts to inadequate information to confidently assess the carcinogenic potential of PFDA for any route of exposure. Accordingly, consistent with USEPA guidance (USEPA 2005) to apply a standard descriptor as part of the hazard narrative and to express a conclusion regarding the weight of evidence for the carcinogenic hazard potential, a descriptor of *inadequate information to assess carcinogenic potential* is clearly scientifically justified. The lack of adequate carcinogenicity data for PFDA precludes dose-response assessment and the derivation of quantitative excess cancer risk estimates (i.e., oral slope factor [SFo], unit risk factor [URF]).

4.3 Summary of the Chronic Values

The chronic evaluation resulted in the derivation of the following values:

- RfD = 2.0E-07 mg/kg-d for PFDA, 2.1E-07 mg/kg-d for ammonium perfluorodecanoate, sodium perfluorodecanoate, and potassium perfluorodecanoate.

The RfD will be used for remediation as part of the Texas Risk Reduction Program (TRRP).

Chapter 5 References

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Appendix 1 Systematic Review and Evidence Integration

TCEQ performed a systematic review of the toxicology and epidemiology literature for 16 PFAS, including PFOA and PFOS. The purpose of this systematic review was to identify relevant toxicology and epidemiology literature to support the development of toxicity factors as per the *TCEQ Guidelines to Develop Toxicity Factors* (TCEQ 2015). The goal was to document the derivation of inhalation toxicity factors (ReVs, ESLs) if inhalation toxicity data were available, and derivation of oral toxicity factors (RfDs, SFos) based on relevant oral studies.

The systematic review is documented in *Systematic Review and Evidence Integration for 16 Perfluoroalkyl and Polyfluoroalkyl Substances (PFAS)* (TCEQ 2025). That document includes the protocols for the systematic evidence map and the systematic review. Briefly, based on the appropriate search terms for the 16 PFAS, a literature search was conducted in PubMed. The literature was screened at the title and abstract stage using DistillerSR. References were further categorized by species, outcomes, duration, and route. For PFDA, the number of references at this stage of screening was 365. The full text of the references included after categorization was further screened. Following full text review there were 10 animal toxicity studies and 1 epidemiology study that were included for PFDA. Data extraction and study quality evaluation were conducted for the PFDA references that were included after the full text review. Data extraction and study quality evaluation were documented in DistillerSR.

The information about the systematic evidence map and systematic review (with data extraction and study quality evaluation for all included studies) was exported from DistillerSR into Excel workbooks. The material in these workbooks was used to inform selection of studies for derivation of toxicity factors for PFDA. Further information can be found in TCEQ (2025).

Appendix 2 Reference Dose for PFDA Derived by USEPA

TCEQ determined that epidemiologic studies are insufficient for dose-response assessment and derivation of a reference dose for PFDA.

USEPA derived the candidate RfDs for PFDA (see Table 5-12 of USEPA 2024) based on several epidemiological studies (i.e., Grandjean et al. 2012, Budtz-Jørgensen and Grandjean 2018, Wikström et al. 2020). USEPA (2024) selected an overall RfD of 2E-09 mg/kg-d based on decreased serum antibody concentrations and decreased birth weight in humans. These RfDs are provided in Table 5.

Table 5. Basis for Reference Dose for PFDA Derived by USEPA

Chemical	RfD	Critical Effect(s), Critical Study/Studies
PFDA	2×10^{-9} mg/kg-d	Decreased antibody concentrations for both tetanus and diphtheria in children at age 7 yr and PFDA measured at age 5 yr (Grandjean et al. 2012, Budtz-Jørgensen and Grandjean 2018)
PFDA	2×10^{-9} mg/kg-d	Decreased birth weight in male and female children (Wikström et al. 2020)

These RfDs are controversial and not scientifically defensible because they are based on flawed epidemiological data.

While epidemiological data may be appropriate for hazard identification, TCEQ has determined that due to weaknesses and limitations of the epidemiological study evidence, the associated epidemiologic results (e.g., potential immunotoxicity and birth weight effects) are not sufficient for quantitative risk assessment and toxicity factor (e.g., RfD) derivation for PFDA. This determination is supported by conclusions of the Agency for Toxic Substances and Disease Registry (ATSDR; part of the U.S. Department of Health and Human Services), the Australian Government (Australian NHMRC 2024, FSANZ 2021), and a number of earlier opinions from national agencies and bodies such as the Danish EPA (2016), the Expert Health Panel for PFAS (2018), and Kirk et al. (2018).

Here we include a discussion of the critical epidemiology-based effects selected for the RfD for PFDA (i.e., antibody responses to vaccination, decreased birth weight) and the reasons why they are not suitable for RfD derivation.

Epidemiology Studies of Immune Effects

The epidemiological studies relied upon by USEPA provide inconsistent evidence about vaccine responses in children and do not demonstrate any clear adverse effect.

USEPA (2024) used epidemiology studies reporting decreased antibody titers in children living on the Faroe Islands (remote islands located in the North Atlantic Ocean and part of the country of Denmark) as evidence of immunotoxicity and as a basis of the RfD for PFDA.

In their October 2024 Public Consultation Draft for Per- and Poly-Fluoroalkyl Substances (PFAS), the Australian Government's National Health and Medical Research Council[b] (Australian NHMRC 2024; see their document for the references cited in the quotation below) concluded the following regarding the use of epidemiological studies for immunotoxicity [*emphasis added*]:

> Some international assessments have derived benchmarks for PFOA using benchmark doses calculated from low levels of PFAS (as a mixture including PFOA) in serum associated with decreased vaccine antibody formation in children (Abraham et al. 2020, Budtz-Jorgensen and Grandjean 2018, Grandjean et al. 2012, Timmerman et al. 2022). Based on a critical evaluation of these studies (SLR 2024a, b, c), and *consistent with the conclusions reached by FSANZ (2021), it was concluded that a causal relationship between increased PFAS serum levels (as a mixture including PFOA) and impaired vaccine response cannot be established with reasonable confidence from the available human epidemiological information*. A number of limitations of the studies (such as small sample size, limited dose-response information and potential confounding by other known environmental immunotoxicants) were identified. *The evidence for an association between increasing PFAS serum levels and impaired vaccine response was found to be insufficient for the endpoint to be used for derivation of a PFOA health-based guideline value*. Although the reduced antibody response following vaccination has been considered by some international assessments as a robust end point to derive a guidance value, it is unclear whether this correlation results in increased rates of infection and hence the clinical implications are uncertain (SLR 2024a, b; FSANZ 2021).

TCEQ agrees that a causal relationship between increased PFAS serum levels and impaired

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[b] Available at: https://consultations.nhmrc.gov.au/environmental-health/australian-drinking-water-guidelines-2024-pfas/; see the fact sheet for the cited quote at: https://www.nhmrc.gov.au/sites/default/files/documents/attachments/water-PFAS/DRAFT-PFAS-Chemical-fact-sheet.pdf

vaccine response cannot be established with reasonable confidence, and that consequently the evidence for an association between increasing PFAS serum levels and impaired vaccine response is insufficient to support derivation of health-based guideline values (e.g., RfDs) for PFAS, including PFDA. Specifically, TCEQ's concerns regarding immunotoxicity endpoints (e.g., decreased antibodies) are due to:

- Inconsistencies and lack of significance of results,
- Inappropriate determinations about adversity of the critical effect,
- Lack of adequate consideration of/adjustment for confounding effects of exposure to other PFAS, and
- Inconsistent, weak evidence that immunotoxicity leads to increased incidences of disease.

Although these issues are applicable to multiple PFAS chemicals that have been included in these studies, these comments will focus on PFDA as they are the subject of the current DSD and the assessments herein.

Findings from Antibody Titer Papers

There is inconsistent significance of findings from antibody titer papers.

The studies principally cited for the immunotoxicity effects are Grandjean et al. (2012) and Grandjean et al. (2017a,b), along with Budtz-Jørgensen and Grandjean (2018). These studies show inconsistency in terms of statistically significant relationships between PFDA serum concentrations and antibody titers, depending on the particular set of variables being explored. For example, even without considering confounding (e.g., by correlated PFAS co-exposures), for PFDA, 3/4 odds ratios (ORs) for PFDA and antibody concentrations falling below the generally considered protective level of 0.1 IU/mL (cited by the study authors) for tetanus and diphtheria in children ages 5 years (n=510) or 7 years (n=386) contain 1, indicating that the weight of evidence (WOE) from this study relied on by some assessments (e.g., USEPA 2024) is for no statistically significant associations with less-than-protective serum antibody concentrations in children (see eTable 4 of Grandjean et al. 2012).[c] Consistent with this, the more recent Grandjean et al. (2017a) study itself states [*emphasis added*] that, "With many antibody concentrations being close to the assumed clinically

[c] The confidence interval (CI) for the one statistically significant OR of 1.36 (age 5, diphtheria) is (1.04, 1.77), with the lower end of the CI practically equal to 1 (eTable 4 of Grandjean et al. 2012). Also consistent with a WOE for no statistically significant associations (much less being able to say "effects" as there are problems with causal attribution to PFDA), 6 of 8 confidence intervals (95% CIs) for both tetanus and diphtheria serum antibodies included 0% change per 2-fold increase in maternal and age 5 serum PFDA (see Table 3 of Grandjean et al. 2012).

protective level of 0.1 IU/mL, *logistic regression showed only weak tendencies for antibody levels below the limit to be associated with serum PFAS concentrations*."[d] So even with many antibody concentrations being close to 0.1 IU/mL, there were only "weak tendencies" for PFAS to be associated with antibody levels below that.

The results from Grandjean et al. (2017a) also showed inconsistent results and weakness of the epidemiologic evidence. That study evaluated PFAS serum concentrations collected in children at age 7 and then at age 13 compared with the change in anti-tetanus or anti-diphtheria titers between ages 7 and 13. The study authors looked at associations with antibody titers and concentrations of 5 PFAS (including PFDA). However, the results for PFDA are inconsistent depending on the vaccine type. For example, while there were statistically significant *decreases in diphtheria antibody titers* with increasing PFDA concentrations at age 7 (see Table 4 of the study), there were general trends of *increasing tetanus antibody titers* with increasing PFDA concentrations at age 7 (one association with borderline statistically significance with a p-value of 0.053; see Table 5 of the study). Inconsistent results were also found in linear regression models of changes in anti-diphtheria concentrations at age 13 associated with serum PFAS concentrations at ages 7 and 13, where there were statistically significant decreases in antibody titers associated with serum PFDA at age 7 but not at age 13 (see Table 2 of the study). By contrast, in linear regression models of changes in anti-tetanus concentrations at age 13, there were no statistically significant decreases in antibody titers associated with serum PFDA at age 7 (or age 13), only a borderline statistically significant increase in anti-tetanus concentrations (p-value of 0.054, serum PFDA at age 7, no ER visit; see Table 3 of the study). To conclude from this study that PFDA concentrations have significant adverse effects on antibody titers requires cherry-picking specific results and ignoring others that do not support the conclusion. These results highlight the inconsistency of the study findings and the significant issues with generalizing results to other ages and vaccine responses. Moreover, none of the analyses in Grandjean et al. (2017a) adjust for confounding co-exposures (e.g., PFAS), which even when considered alone precludes use of such epidemiological studies for derivation of scientifically defensible toxicity factors.

Adversity of Antibody Titer Effects

The antibody titer papers use the wrong measure to indicate an adverse effect.

The Grandjean et al. studies use a titer level of 0.1 IU/mL to indicate a threshold below which

[d] Also, while Grandjean et al. (2017b) state that, "At age 5, 152 (44%) children had antibody concentrations lower than the protective level of 0.1 IU/mL for diphtheria and 126 (36%) for tetanus", this appears inconsistent with Table 1 of that study, which shows that the 25th percentiles for diphtheria and tetanus serum antibody concentrations were 0.1 IU/mL.

there is no longer full clinical protection against viral infection. However, the level of serum antibodies corresponding to a clinically protective level is assay-specific, and it appears that Grandjean et al. merely cited a commonly used protective value (0.1 IU/mL) that is actually 10-fold higher than the assay-specific protective level (0.01 IU/mL) for the assay that was used in the study.[e] More specifically, for the toxin binding inhibition (ToBI) assay apparently used in the Grandjean Faroe Islands studies, ≥ 0.01 IU/mL is considered to be clinically protective, not the value of ≥ 0.1 IU/mL indicated by study authors.[f] *This means that the reported associations for decreases in serum antibodies (already inconsistent and confounded by co-exposures) are even less likely to be considered adverse relative to the 10-fold lower assay-specific protective level (0.01 IU/mL)*. This is not surprising given the rarity of tetanus/diphtheria cases, particularly in those who are fully vaccinated, and the inconsistent, weak epidemiologic evidence on increases in the incidences of diseases based on the epidemiological literature (discussed below). These issues bring into serious question the validity of any assumptions regarding the adversity of these associated serum antibody decreases, regardless of the instances of statistical significance.

The World Health Organization (WHO 2018) also discusses and illustrates the timing of primary and booster vaccinations and durations of protection in the context of the minimum putatively protective level of 0.01 IU/mL (pp. 14-15 of WHO 2018). Thus, the protective level cited by Grandjean et al. (2012) for the assay used in their study is 10-fold higher than the protective level cited by WHO (2017, 2018), further calling into question assumptions concerning the adversity of the reported results.

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[e] This is also relevant to statements from USEPA for PFOA and PFOS such as, "For diphtheria and tetanus, a clinically significant decrease would be a decrease that brought a person's antibody concentration below the level thought to provide protection. Generally, that would be 0.1 IU/mL (WHO 2017, Cellesi et al. 1989, Galazka and Kardymowicz 1989). If a person had a concentration above 0.1 IU/mL but a 5% decrease brought their concentration below 0.1 IU/mL, that would be clinically significant. Depending on the population, there might be a large number of persons (30–40%) with antibody concentrations close to 0.1 IU/mL (Zasada et al. 2013, Hanvatananukul et al. 2020, Yusoff et al. 2021, Khetsuriani et al. 2013)." (see Section 4.1.6 of USEPA 2021a,b). Additionally, the last references cited by USEPA refer to seroprevalence in Poland, Thailand, Malaysia, and Tajikistan, which is not representative of the seroprevalence in the United States (Liang et al. 2018). In some underdeveloped countries outbreaks of tetanus and diphtheria occurred in the 1980s and 1990s, probably because these countries do not have the herd immunity and vaccination programs with boosters in place as does the United States. The incidence rates for tetanus and diphtheria are lower in the United States when compared to those of Poland, Thailand, Malaysia, and Tajikistan.

[f] Grandjean et al. (2012) reported that "serum concentrations of antibodies against the tetanus toxoid were measured in coded samples by the Statens Serum Institut using enzyme-linked immunosorbent assay…", citing Hendriksen et al. (1988) who describe the ToBI assay as a modified ELISA, and WHO (2017) indicates that for a modified ELISA the clinical protection is achieved at ≥ 0.01 IU/mL, not ≥ 0.1 IU/mL as indicated by Grandjean et al.

Confounding by Other PFAS

The antibody titer papers do not control for simultaneous co-exposure to multiple PFAS compounds.

In regard to confounding co-exposures in this same birth cohort of 656 children (e.g., Grandjean et al. 2012, 2017a), PFDA was correlated with other PFAS (e.g., Pearson correlation coefficients of 0.35-0.78 for PFOS, PFOA, PFNA) that had some statistically significant associations with antibody concentrations falling below the protective level of 0.1 IU/mL (see Table 2 and eTable 4 of Grandjean et al. 2012).[g] Thus, for PFDA, as well as the other PFAS included in these studies, confounding co-exposures that have not/cannot be adequately adjusted for are likely to be a significant issue affecting reported results.

The authors of these studies include discussion regarding confounding and the ability/inability to causally attribute associated effects to any specific PFAS compound:

- Grandjean et al. (2012) state [*emphasis added*], "Although all of the 5 PFCs [perfluorinated compounds] measured showed negative associations with antibody levels, the overlapping confidence intervals and the lack of comparative toxicology studies *prevent inference in regard to causal attribution*… PFOS (most likely the linear isomer) and PFOA appear to be the main culprits."

- The more recent Grandjean et al. (2017a) study states [*emphasis added*], "Owing to the *intercorrelations between the serum PFAS* concentrations, further analysis of *the possible role of individual PFASs was not pursued*, and *the observed associations may reflect the effects of the PFAS mixtures*."

- Similarly, Grandjean et al. (2017b) state [*emphasis added*], "The close correlations *prevented meaningful adjustment* for concomitant PFAS exposures."

Thus, it appears that effects may neither rise to the level of adversity (e.g., decreases to below the assay-specific protective level of 0.01 IU/mL), nor be attributable specifically to any of the studied PFAS, including PFDA. Co-exposures to other PFAS (at a minimum) that have not or cannot be adequately accounted for in the analyses are likely to be significant confounders in these epidemiological studies, especially because PFAS exposures are correlated, they are chemically-similar compounds, and there appears to be little variation in exposure (i.e., low

[g] A 2-fold increase in PFOS and PFOA concentrations at age 5 years was associated with odds ratios between 2.38 (95% CI, 0.89 to 6.35) and 4.20 (95% CI, 1.54 to 11.44) for falling below a clinically protective level of 0.1 IU/mL for tetanus and diphtheria antibodies at age 7 years.

exposure contrasts) for the single PFAS being assessed (e.g., Table 2 of Grandjean et al. 2012, Table 1 of both Grandjean et al. 2017a and 2017b). For example, Grandjean et al. (2012) shows that PFOA and PFOS had a correlation coefficient of 0.5 in the blood sera of 5-year olds and interquartile range (IQR) differences in blood sera concentrations of less than 1.6-fold each (e.g., 75th percentile blood concentration of PFOA/25th percentile blood concentration of PFOA), and PFDA and PFNA had a correlation coefficient of 0.78 in the blood sera of 5-year olds and IQR differences in blood sera concentrations of less than 1.9-fold each (see Table 2 of the study).

Despite Grandjean et al. (2017b) stating that the close correlations prevented meaningful adjustment for concomitant PFAS exposures, Budtz-Jørgensen and Grandjean (2018) attempted to do just that to derive PFAS-specific benchmark doses (BMD) for dose-response assessment. Some of the results of that analysis help demonstrate the potential effects of confounding co-exposures when attempts are made to adjust for them. Table 2 of Grandjean et al. (2017b) reports the change (in percent) of the pre-booster serum-antibody concentrations at age 5 years associated with a doubling of the serum concentration of PFDA. Results for cohorts 5, 3, and joint results are in the negative direction for tetanus antibodies at age 5 but *none are statistically significant*, which already points to the unreliability of an effect having been demonstrated by these results and the unreliability of any RfD based on these results or association. Table 2 of Budtz-Jørgensen and Grandjean (2018) reports BMD results for the five prenatal PFAS concentrations, including PFDA, on antibody concentrations at age 5 years (pre-booster) both unadjusted and adjusted for PFOS/PFOA co-exposures. For tetanus antibodies, while unadjusted BMDs for three models for PFDA (linear, piecewise, conservative) appear to show excellent agreement (BMDs of 0.11-0.25 ng/mL) with insignificant reliance on choice of model, when adjusted for PFOS/PFOA the three models' best estimates of the PFDA serum concentrations associated with a 5% change go to infinity (∞; although BMDLs can still be estimated). That is, all three tested models were unable to reasonably fit the data when adjusting the PFOS/PFOA (the generated BMDs = infinity). For diphtheria antibodies, Table 2 of Grandjean et al. (2017b) reports statistically significant changes for cohort 3 and joint results for the pre-booster serum-antibody concentrations at age 5 years associated with a doubling of the serum concentration of PFDA. However, similar to results for tetanus antibodies, Table 2 of Budtz-Jørgensen and Grandjean (2018) reports that when BMD results are adjusted for PFOS/PFOA, two of the three models' best estimates of the PFDA serum concentrations associated with a 5% change go to infinity (∞; although BMDLs can still be estimated). That is, two of three tested models were unable to reasonably fit the data when adjusting the PFOS/PFOA (the generated BMDs = infinity). While Table 1 of Budtz-Jørgensen and Grandjean (2018a; BMD results for the age-5 serum concentrations of five PFASs in regard to tetanus and diphtheria antibody concentrations at age 7 years) provides no BMDs for PFDA that go to infinity (∞), Table 2 results point to the unreliability of

this endpoint and this has been considered along with the other issues raised.[h]

BMD results from USEPA's PFDA assessment (USEPA 2024) demonstrate the importance of co-exposures to other PFAS. Tables C-1 and C-3 of the draft assessment (below) provide BMD results for critical antibody effects used for USEPA's RfD derivation (e.g., see Table ES-1).

Table C-1. Results specific to the slope from the linear analyses of PFDA measured in serum at age 5 years and $\log_2$(tetanus antibody concentrations) measured at age 7 years in a single-PFAS model and in a multi-PFAS model from (Budtz-Jørgensen and Grandjean, 2018b)

Exposure	Model shape	PFOS and PFOA adjusted	Slope (β) per ng/mL in serum	SE(β) ng/mL in serum	Slope (β) fit	Lower bound slope (β_{LB}) per ng/mL in serum
PFDA at age 5 yr	Linear	No	−1.55	0.602	$p = 0.01$	−2.55
PFDA at age 5 yr	Linear	Yes	−0.98	0.681	$p = 0.15$	−2.10

2

PFOS and PFOA had correlation coefficients of 0.39 and 0.35 with serum PFDA at age 5, respectively (Table 2 of Grandjean et al. 2012). Despite these relatively low correlation coefficients (Mukaka 2012), Table C-1 shows that just controlling for co-exposures from these two PFAS (PFOS, PFOA) resulted in significant impacts on slope (β) and slope fit. The slope estimate for PFDA was reduced 37% and *PFDA is no longer a significant predictor of tetanus antibody concentrations* (p=0.15). The most likely explanation (Occam's razor) is classic confounding as PFOS and PFOA are documented immunotoxicants (e.g., per Budtz-Jørgensen and Grandjean 2018a), and the existence of some chance that correction for these co-exposures could create some confounding is not a scientifically robust justification for dismissing the important implications of the results of adjustments for PFOS/PFOA that the study authors themselves (Budtz-Jørgensen and Grandjean 2018) thought it important to adjust for, and with good reason. *These results demonstrate the statistical unreliability of serum PFDA predicting tetanus antibody concentrations when just two other PFAS are controlled for*. Table C-3 from USEPA (2024) concerns the USEPA RfD critical effect based on diphtheria antibody concentrations.

[h] For example, the odds ratios for PFDA and inadequate antibody concentrations for diphtheria and tetanus at 7 years were not statistically significant (see eTable 4 of Grandjean et al. 2012).

Table C-3. Results specific to the slope from the linear analyses of PFDA in serum measured at age 5 years and $\log_2$(diphtheria antibodies) measured at age 7 years from Table 1 in a single-PFAS model and in a multi-PFAS model from (Budtz-Jørgensen and Grandjean, 2018b)

Exposure	Model shape	PFOS and PFOA adjusted	Slope (β) per ng/mL in serum	SE(β) ng/mL in serum	Slope (β) fit	Lower bound slope (β_{LB}) per ng/mL in serum
PFDA at age 5 yr	Linear	No	−0.894	0.561	$p = 0.11$	−1.82
PFDA at age 5 yr	Linear	Yes	−0.297	0.635	$p = 0.64$	−1.35

The implications of these results are worse. First, even when evaluated alone without accounting for co-exposures to relatively low correlated PFOS and PFOA, serum PFDA is not a significant predictor of diphtheria antibody concentrations (p=0.11). Table C-3 further shows that controlling for co-exposures from these two PFAS (PFOS, PFOA) resulted in significant impacts on slope (β) and slope fit. *The slope estimate for PFDA was reduced 67% and serum PFDA became a worse nonsignificant predictor of diphtheria antibody concentrations (p=0.64)*. The most likely explanation (Occam's razor) is classic confounding as PFOS and PFOA are documented immunotoxicants (e.g., per Budtz-Jørgensen and Grandjean 2018), and the existence of some chance that correction for these co-exposures could create some confounding is not a scientifically robust justification for dismissing the important implications of the results of adjustments for PFOS/PFOA that the study authors themselves (Budtz-Jørgensen and Grandjean 2018) thought it important to adjust for, and with good reason. *Thus, when co-exposures are taken into account for two modestly correlated PFAS (PFOS, PFOA), serum PFDA is not a significant (i.e., reliable) predictor of these critical effects serving as a basis of the USEPA (2024) RfD (i.e., decreases in serum tetanus and diphtheria antibody concentrations)*.[i]

The inability of these USEPA (2024) models to generate BMD modeling results for serum PFDA as a statistically significant predictor of tetanus and diphtheria antibodies when adjusting for PFOS/PFOA demonstrates the potential for confounders (e.g., other PFAS) to significantly affect results when adjusting BMDs for just a few co-exposures. The bottom line is that results for PFDA associations with these serum antibody endpoints (and BMDs) that adequately account for other relevant co-exposures (e.g., numerous PFAS) are not available, and as mentioned above, PFDA was correlated with other PFAS (e.g., coefficients of 0.35-0.78 for PFOS, PFOA, PFNA) that had some statistically significant associations with antibody

[i] Knowing this, disparate results are not particularly surprising, such as the 18.7% increase in tetanus antibodies predicted for children (age 13) with a 2-fold increase in serum PFDA based on the same study and type of analysis used for the RfD critical effects (see Table 3-12, p. 3-59 of USEPA 2024).

concentrations falling below the study author-cited protective level of 0.1 IU/mL (see Table 2 and eTable 4 of Grandjean et al. 2012) but were not accounted for in the Budtz-Jørgensen and Grandjean (2018) BMD adjustments. *Thus, confounding co-exposures have not been adequately accounted for in the relevant analyses for PFDA, which should be considered along with the other issues raised*. Therefore, any effects observed may be considered, at best, mixture effects. While real-world exposures are to mixtures of chemicals, it is not scientifically defensible, accurate, or realistic to attribute the effects of a mixture of very similar chemicals to a single component (i.e., co-exposures to other components of the mixture contributing to the observed effects would have to be able to be adequately adjusted for).[j]

USEPA inappropriately uses PFDA BMD/BMDL estimates from models that do not control for confounding co-exposures (e.g., PFOS/PFOA) and justifies this decision by arguing (without evidence) that controlling for confounding will cause confounding.

Classic confounding is likely for PFDA epidemiologic results because PFAS exposures are correlated, they are chemically similar compounds, and some are potential immunotoxicants (e.g., Budtz-Jørgensen and Grandjean 2018). To justify their decision to use estimates that are not controlled for confounders, USEPA (2024) suggests that correction for PFAS co-exposures could create confounding. However, the possibility of this occurring to some unknown extent is not a scientifically robust justification for dismissing out-of-hand the obvious importance of adjusting for these co-exposures. Such adjustments are recognized as important by the study authors of Budtz-Jørgensen and Grandjean (2018), and they did not indicate any concerns about creating confounding by adjusting for correlated co-exposures (PFOS and PFOA). USEPA (2024) appears to selectively cite this concern about creating confounding (based on Weisskopf et al. 2018 and Weisskopf and Webster 2017) in an attempt to provide some rationale for dismissal of the co-exposure-controlled results and to justify selection of BMDLs uncontrolled for PFOS and PFOA co-exposures. When controlling for PFOS/PFOA in BMD modeling, the following changes result for PFDA-associated effects: slope (β) values are reduced; serum PFDA is a nonsignificant predictor (or even worse nonsignificant predictor) of tetanus and diphtheria antibody concentrations (see Tables C-1 and C-3 above from USEPA 2024).

In contrast to the final assessment for PFDA (USEPA 2024), USEPA's draft assessments for PFOA and PFOS (EPA 2021a,b) do not express any similar concerns about creating

[j] For example, just as there are thousands of PFAS, there are numerous hydrocarbon components of gasoline that people are exposed to as a mixture, and even though they number fewer than the number of PFAS, it still would not be scientifically defensible to derive a toxicity factor for just one component, toluene for example, attributing the totality of the mixture effects observed solely to toluene following exposure to gasoline (e.g., even if two co-exposures such as ethylbenzene and xylenes were adjusted for).

confounding by adjusting PFOS or PFOA results for co-exposures and do not cite Weisskopf et al. (2018) or Weisskopf & Webster (2017). Weisskopf et al. (2018) indicates: (1) sometimes, depending on causal structure, the inclusion of multiple exposure variables in a model can amplify the amount of bias in a regression estimate compared to analyzing single exposures; and (2) this potential amplification of biases increases with stronger correlations between mixture components. To demonstrate that this can occur in some cases, the study authors used "highly correlated exposures" (e.g., r^2=0.9), whereas the correlation coefficients between PFDA and the other PFAS examined are low-to-moderate (e.g., low correlation coefficients of 0.35 and 0.39 for PFOA and PFOS, respectively, and a moderate coefficient of 0.78 for PFNA (Grandjean et al. 2012); Mukaka 2012). The results of Weisskopf et al. (2018) do not constitute reasonable doubt for PFDA or other PFAS, that the potential amplification of biases that might be caused by adjusting for these correlated co-exposures is significantly greater than the potential amplification of biases that might be caused by not adjusting for them. Further, the presence of the former confounding remains undemonstrated under the same or similar circumstances. Co-exposures (e.g., various correlated PFAS) need to be adequately adjusted to reduce classic confounding. Most of the relevant analyses for PFOS and PFOA have not adequately accounted for these co-exposures, and when some adjustment has been applied, the results of the analyses have largely been ignored. *Indeed, USEPA acknowledges that it is plausible that the observed associations with PFAS exposure (e.g., PFOS, PFOA) could be explained by confounding across the PFAS (see Section 3.3.4.1.1 of USEPA 2021a,b) and that uncertainty remains concerning the Grandjean et al. study results due to such confounding (e.g., pp. 3-73 and 3-106 of USEPA 2024).* Again, this issue calls into question the validity of the conclusions drawn from these studies by USEPA, and the risk estimates derived from them.

Ground-Truthing Vaccine Findings Using Disease Rates

USEPA acknowledges that the evidence across studies for associations between PFDA and changes in disease rates (i.e., increased disease presumably due to diminished immunity) is inconsistent overall and does not provide coherence with the observed antibody response effects, stating possibly because PFDA-associated decreases in antibody response were too limited to result in the more downstream infectious disease effects (pp. 3-76 and 3-77 of USEPA 2024).

Regarding potential immunosuppression by PFDA, effects that rise to the level of adversity would be expected to result in *increased incidences of disease*, reflecting lower immunity and lower resistance to disease in the real world. However, consistent with the inconclusive evidence from the Grandjean et al. antibody titer studies (e.g., lack of statistically significant associations, judgments of adversity made using a protective level of 0.1 IU/mL instead of the appropriate assay-specific protective level of 0.01 IU/mL [see discussion above]), there is little

evidence of an association with disease. Almost all odds ratios (ORs) in Table 3-12 of USEPA (2024) include 1, indicating that *the WOE from studies on PFDA and infectious disease in humans is for no statistically significant associations*. Consistent with this, host resistance was unaffected by PFDA based on the limited animal study data available, and host resistance assays are considered highly relevant to the evaluation of immunotoxicity in the context of human health assessment (USEPA 2024, IPCS 2012).

The inconsistent evidence from studies on infectious disease in humans, resulting in a WOE for no statistically significant associations, is of obvious relevance to judgment concerning the adversity of the antibody concentration decreases associated with PFDA in epidemiologic studies. *Weighing considerations relevant to adversity (e.g., inconsistency in epidemiological study results for statistically significant antibody levels below the protective level(s)) and co-exposure confounding (e.g., by other PFAS) in relevant epidemiological studies results in TCEQ weighing the human evidence as weak in regard to potential PFDA associations with immunosuppressive effects (reduced antibody levels) resulting in demonstrable adverse effects (i.e., statistically increased incidences of diseases) attributable specifically to PFDA exposures*.[k] The statements cited above from Grandjean et al. regarding problems with causal attribution to specific PFAS support this determination as well.

Moreover, it is noted that the USEPA-estimated points of departure (PODs) (highest doses at which immunosuppressive effects do not occur) based on these epidemiological studies range from 2.57E-04 mg PFDA/L blood serum to 7.02E-04 mg PFDA/L blood serum ($BMDL_{1/2\ SD}$ values from Table 5-10 of USEPA 2024).[l] For the corresponding levels that are estimated to be associated with immunosuppressive effects (i.e., the BMDs associated with the BMDLs cited above), the blood sera concentrations range from 3.85E-04 to 2.26E-03 mg/L for PFDA (Table C-9 of USEPA 2024). When intrahuman variability is considered (through application of a UF_H of 10), the resulting BMDL-based POD values range from 2.57E-05 to 7.02E-05 mg PFDA/L blood (0.0257 to 0.0702 µg PFDA/L blood serum), and the resulting BMD-based POD values range from 3.85E-05 to 2.26E-04 mg PFDA/L blood (0.0385 to 0.226 µg PFDA/L blood serum). Data from NHANES show that geometric means (GMs) representative of the U.S. population are well above most of these blood serum levels (see Appendix 3).[m] For example, 2005-2018 population GMs for PFDA range from 0.154-0.355 µg/L, which are higher than the PODs

[k] By contrast, laboratory animal studies are not plagued by confounding due to significant co-exposures to correlated, chemically similar compounds (e.g., PFAS).

[l] Based on $BMD_{1/2\ SD}$ values (Table C-9, p. C-16), these values are 0.385 to 2.26 µg PFDA/L blood serum.

[m] See NHANES Biomonitoring Data Tables at https://www.cdc.gov/exposurereport/data_tables.html. Budtz-Jørgensen and Grandjean (2018a) also acknowledge that, "Our BMDL results, both before and after adjustment are generally below current exposure levels…"

adjusted for intrahuman variability (cited above) and encompass the upper end of the BMD range adjusted for intrahuman variability (cited above). That is, this NHANES GM range for the U.S. population is 2.2- to 13.8-fold higher than the BMDL-based PODs (analogous to NOAELs) adjusted for intrahuman variability, as well as bracketing the upper end of the BMD-based POD range (analogous to LOAELs) adjusted for intrahuman variability. Despite the fact that PFDA serum levels in the general U.S. population exceed the levels at which antibody titers from vaccines could be suppressed based on results and conclusions from USEPA (2024), tetanus and diphtheria are very rare in the U.S. population. The average annual number of tetanus cases in the U.S. from 2009-2018 was 29, with the CDC attributing most cases to individuals who either had not been vaccinated or who were not current on their boosters (e.g., only 3% of the cases from 2001-2008 were in people who had received a complete tetanus toxoid series with the last dose within 10 years; Tiwari et al. 2021). Tetanus also appears to be particularly rare in U.S. children, as it occurs primarily in older adults. Per Liang et al. (2018):

> "During 2001-2016, three neonatal tetanus cases and 459 non-neonatal tetanus cases were reported to the National Notifiable Diseases Surveillance System (NNDSS). The median age for non-neonatal cases was 44.0 years (range: 2-95 years)… The risk for both tetanus disease and mortality was higher among persons aged ≥65 years than among persons aged <65 years. Tetanus occurs almost exclusively among persons who are unvaccinated or inadequately vaccinated or in those whose vaccination histories are unknown or uncertain."

More current data show the same trends in incidences of tetanus in the U.S. (Available at: https://www.cdc.gov/surv-manual/php/table-of-contents/chapter-16-tetanus.html)

> "From 2013 through 2022, a total of 267 cases from tetanus were reported in the United States through the National Notifiable Diseases Surveillance System (NNDSS) … Vaccination status was known for 67 (25%) tetanus cases reported from 2013 to 2022. Only 16 (24%) were reported to have received three or more doses of tetanus toxoid-containing vaccines. The remaining patients were either unvaccinated or had received fewer than three doses of tetanus toxoid. Of the 267 cases of tetanus, 54 (20%) were in people 65 years of age or older, 162 (61%) were in people 20 through 64 years of age, and 51 (19%) were in people younger than 20 years, including 1 case of neonatal tetanus."

The incidence of U.S. diphtheria cases is even more rare. The CDC reported only 14 cases total

from 1996 through 2018 (Acosta et al. 2021).[n] *Thus, consistent with the highly uncertain results and weakness of the epidemiology study data discussed above, and despite the NHANES blood serum data showing exceedances of the USEPA (2024) human PODs and BMDs adjusted for intrahuman variability, U.S. disease incidence data do not support the conclusion that PFOA and/or PFOA cause adverse immunotoxicity at the concentrations that are used to derive their respective USEPA RfDs.* That is, U.S. disease incidence data do not support that serum PFDA (or any other serum PFAS) is suppressing tetanus and diphtheria vaccine responses and leaving people (adults or children) vulnerable to infection from these diseases.[o]

Uses for Immune Effects Epidemiology Data

TCEQ considers the epidemiologic evidence on immune effects as possibly relevant for hazard identification but unreliable for dose-response assessment and toxicity factor derivation. This conclusion is consistent with recent assessments by the Australian government and by agencies in the U.S. and other countries.

As discussed above, the Australian government (e.g., FSANZ 2021; see their document for the references they cited below) has concluded that associations of PFAS with immunological endpoints do not provide a suitable basis for quantitative risk assessment [*emphasis added*]:

> "While these studies provide limited evidence of statistical associations, *a causal relationship between increased PFAS blood levels and impaired vaccine response cannot be established with reasonable confidence*. *The evidence* for an association between increasing PFAS blood levels and impaired vaccine response *is insufficient for quantitative risk assessment* on the basis of *substantial uncertainties and limitations* including:
>
> - the small number of studies and participants, and mostly cross-sectional design of studies such that *conclusions around causality should be drawn with caution*.

[n] WHO also provides data on tetanus and diphtheria rates in the U.S., available by country and year at: https://immunizationdata.who.int/global/wiise-detail-page/diphtheria-reported-cases-and-incidence, and https://immunizationdata.who.int/global/wiise-detail-page/tetanus-reported-cases-and-incidence

[o] The apparent lack of adversity/consequence for the effects reported for tetanus and diphtheria certainly does not provide support for an expectation of adversity/consequence for other effects not measured/observed (e.g., for vaccines for other diseases and their incidences).

- limited dose-response information with *most studies investigating a narrow range of blood levels associated with background levels* of PFAS exposure.

- *inconsistency* in antibody response to vaccines between different PFAS congeners *which cannot [be] explained by study design*.

- *potential for confounding* by other known environmental immunotoxicants *such as polychlorinated biphenyls (PCBs) for which inverse associations* with blood serum antibody concentrations against tetanus and diphtheria *have previously been reported in the child populations living in the Faroe Islands* (Heilmann et al. 2010).

- *uncertainty about the clinical relevance, if any, of the observed statistical associations to susceptibility to infectious disease*."

"In summary, new epidemiological studies provide some evidence of statistical associations between PFAS blood levels and impaired vaccine response, increased susceptibility to infectious disease and hypersensitivity responses. However, *the data are insufficient to establish causal relationships* and it *cannot be ruled out with reasonable confidence* that the observed *statistical associations may have been due to confounding, bias or chance*. On the basis of the uncertainties and limitations in the evidence base, *immunomodulation is not currently considered suitable as a critical endpoint for quantitative risk assessment* for PFAS."

FSANZ (2021) adds that this conclusion is consistent with the recent decisions of the German Human Biomonitoring Commission (Hölzer et al. 2021; Schümann et al. 2021), ATSDR (2018, 2021), and a number of earlier opinions from national agencies and bodies such as Danish EPA (2016), Expert Health Panel for PFAS (2018), and Kirk et al. (2018). See FSANZ (2021) for references. The Australian Government has reaffirmed the position that that associations of PFAS with immunological endpoints do not provide a suitable basis for quantitative risk assessment as recently as October 2024 (Australian NHMRC 2024).

Epidemiology Studies of Birth Weight Effects

The epidemiology studies referenced by USEPA (2024) that evaluated the potential for PFDA-associated effects on birth weight report inconsistent results and have inadequate control for confounding.

USEPA uses low birth weight as a co-critical effect, which is an effect routinely recognized as adverse when there is evidence to sufficiently support it. However, Figures 3-29 through 3-31 from USEPA (2024), reproduced below, show that results from epidemiology studies investigating associations between PFDA and birth weight are rarely statistically significant and

may generally indicate either positive or negative associations between PFDA and birth weight. Figures 3-30 and 3-31 even show some statistically significant results for PFDA-associated increased birth weight in males and females, respectively. An appreciable inconsistency in results is obvious upon inspection of these forest plot figures. Taken together, the overall epidemiological WOE for PFDA-induced low birth weight is very poor.

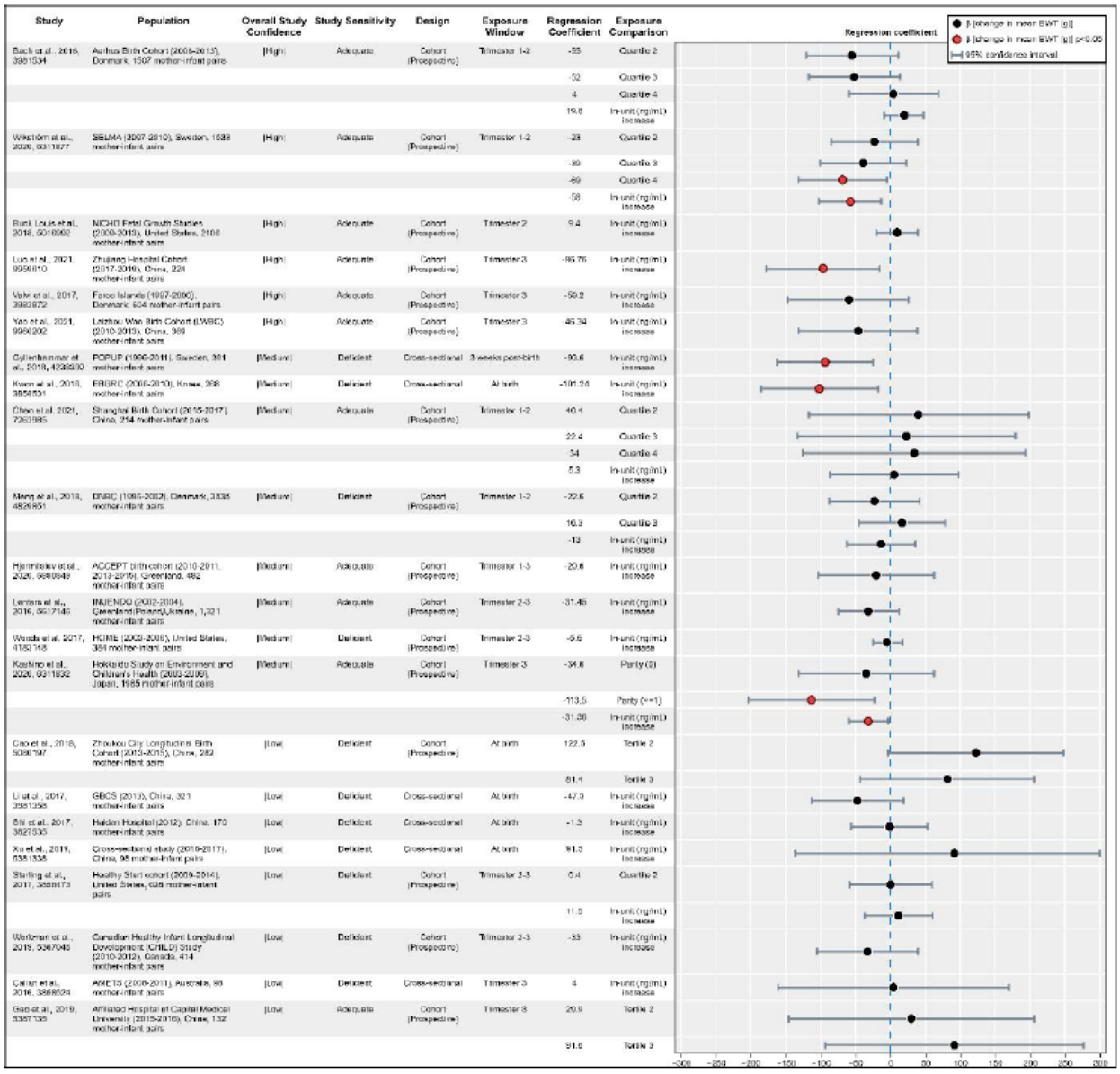

Figure 3-29. Overall study population mean birth weight results for 22 PFDA epidemiological studies.[a–d] (Results can be viewed by clicking the HAWC link.)

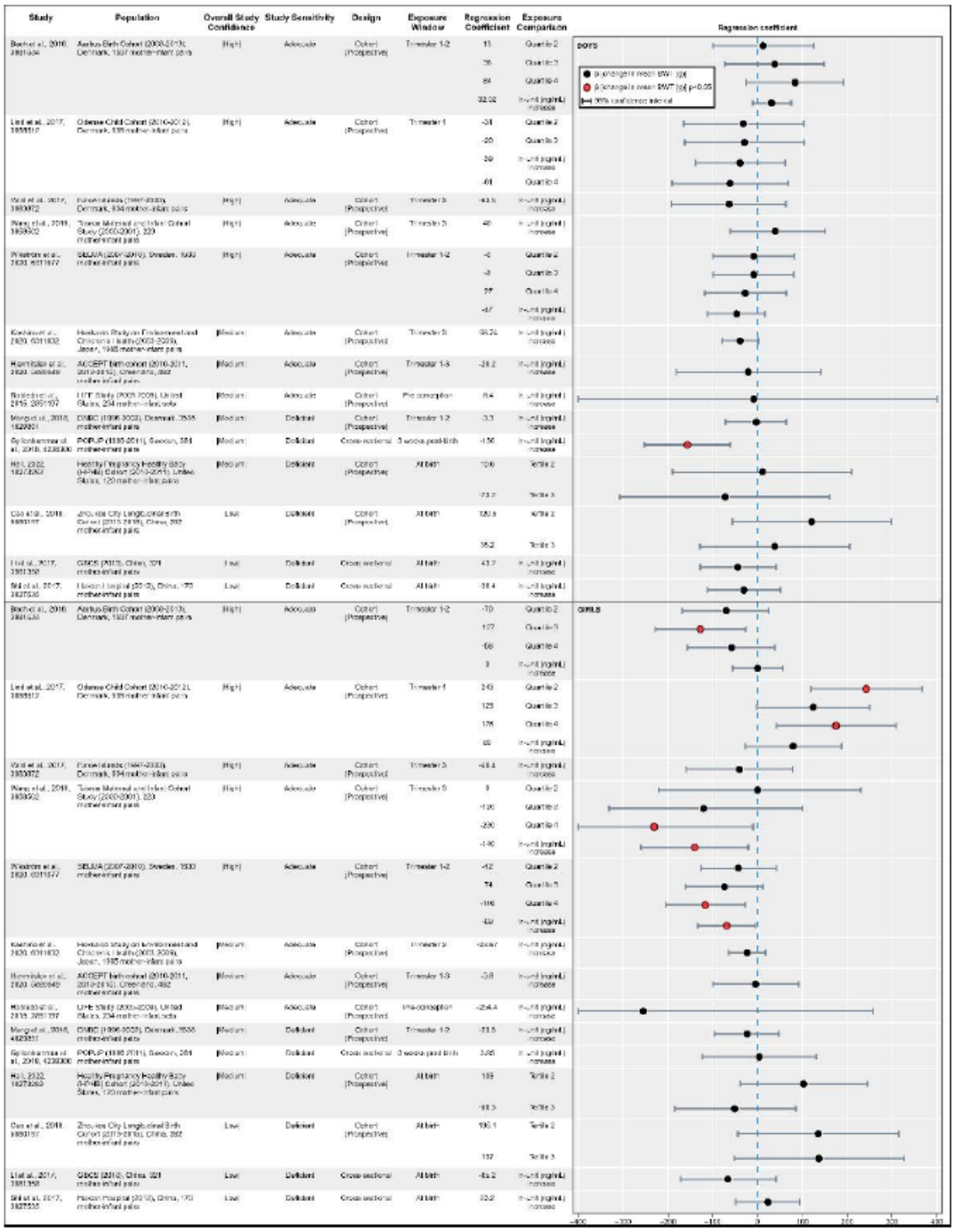

Figure 3-30. Sex-specific male infants only mean birth weight results for 14 PFDA epidemiological studies.[a-e] (Results can be viewed by clicking the HAWC link.)

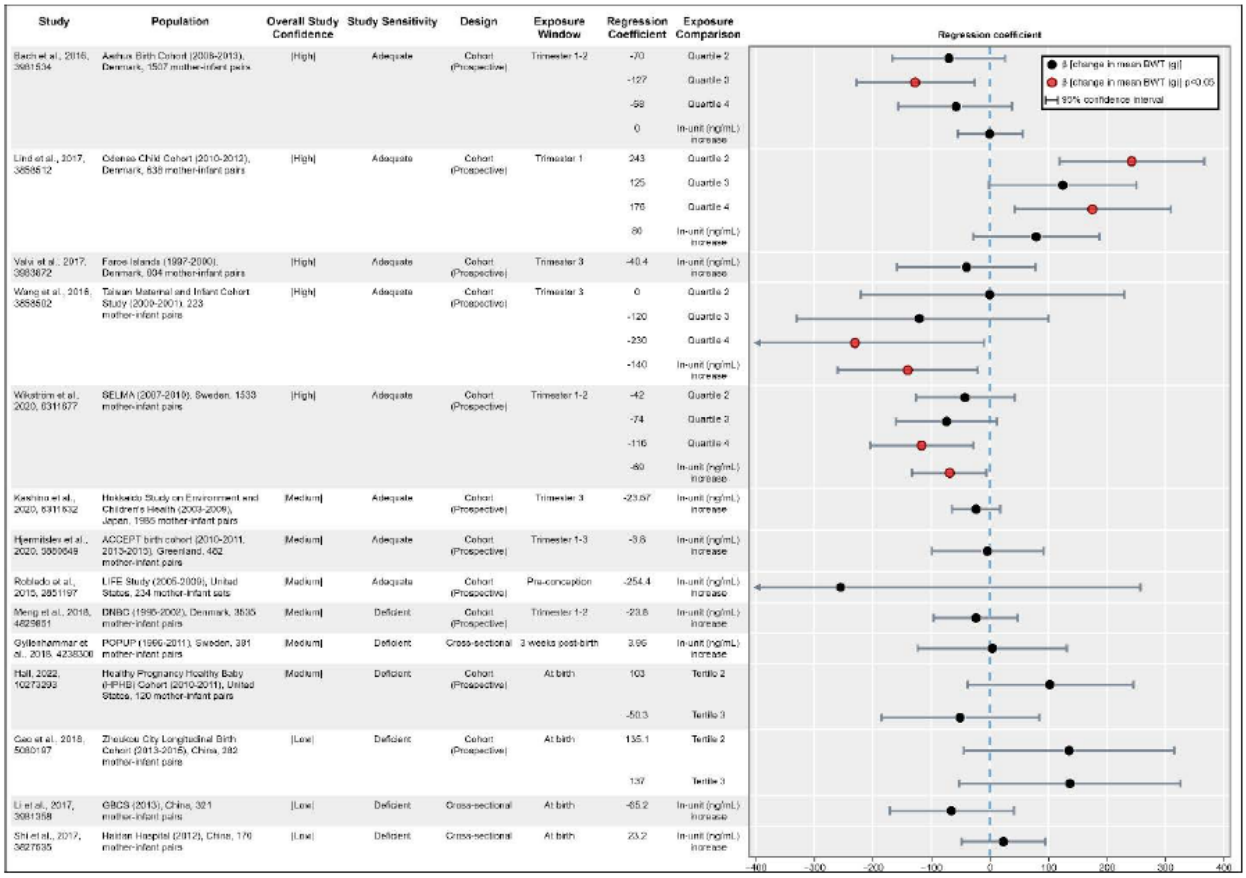

Figure 3-31. Sex-specific female infants only mean birth weight results for 14 PFDA epidemiological studies.[a–f] (Results can be viewed by clicking the HAWC link.)

The Australian government recently reviewed the study underlying the decreased birth weight partial basis for the USEPA's PFDA RfD (i.e., Wikström et al. 2020) to evaluate the scientific reliability of its findings and data (SLR 2024d). The review concluded that the data on dose-response from Wikström et al. (2020) are not sufficiently reliable for use as a key study for derivation of a toxicity factor (e.g., RfD).[p]

Comparison of TCEQ Conclusions to Other Agencies' Conclusions

TCEQ's conclusions are consistent with determinations from national and international governmental agencies.

As recently as October 2024 (Australian NHMRC 2024), the Australian Government has reaffirmed the position that the epidemiology literature (e.g., potential effects on antibody titers, birth weight) is inadequate for use as the basis of deriving toxicity factors for PFAS.[q] TCEQ similarly concurs with ATSDR (2021), which found that the epidemiology literature is inadequate for use as the basis of deriving minimal risk levels (MRLs) for PFAS. ATSDR noted [*emphasis added*]:

"There are sufficient epidemiological data to identify possible sensitive targets for many of the perfluoroalkyls; however, there are *two major limitations to establishing dose-response relationships* for these effects and using the epidemiological studies to derive MRLs: *accurate identification of environmental exposure levels producing increased risk* for adverse effects (exposure estimates and routes of exposure) and *likely co-exposure to mixtures of perfluoroalkyls*. Other limitations include the cross-sectional design of the majority of epidemiological studies and the potential that reverse causality contributes to the observed associations… In summary, the epidemiological databases for several perfluoroalkyls provide valuable information on *hazard identification*; however, *uncertainties regarding doses associated with adverse effects and possible interactions between compounds preclude use of these data to derive MRLs*."

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[p] For example: (1) as a common limitation of epidemiological studies, it was not possible to control for all possible confounders; and (2) none of the children in the study were classified as having low birth weight (< 2,500 g) and thus it is not clear if the association for decreased birth weight found in this study would also be the same for children who are already close to being classified as low birth weight (where the effect would become of potential concern). Considerations such as these indicate that there is still marked uncertainty in terms of the appropriateness of using epidemiological data to define the threshold and dose-response of birthweight effects potentially caused by PFDA exposure.

[q] Fact sheet available at: https://www.nhmrc.gov.au/sites/default/files/documents/attachments/water-PFAS/DRAFT-PFAS-Chemical-fact-sheet.pdf

Based on the totality of available scientific data, TCEQ agrees with the recent conclusions of ATSDR (2021) and the Australian government (FSANZ 2021, Australian NHMRC 2024), that the epidemiology literature (e.g., on PFAS blood levels and impaired vaccine response, decreased birth weight in infants) *is inadequate for quantitative risk assessment and use as the basis for deriving toxicity factors (e.g., RfDs) for PFAS, including PFDA*. This is not to say that PFAS are incapable of causing effects such as those on the immune system (e.g., the epidemiologic data are relevant to hazard identification and there are also laboratory animal data relevant for hazard identification and dose-response assessment), but rather that the epidemiological data are simply insufficient for dose-response assessment due to significant issues discussed in these comments.

Consistent with the discussion above and the conclusions of some other national and international governmental agencies (e.g., ATSDR 2021, FSANZ 2021, Australian NHMRC 2024), TCEQ concludes that:

- The epidemiology literature (e.g., on PFAS blood levels and impaired vaccine response, decreased birth weight in infants) is inadequate for quantitative risk assessment and for use as the basis for deriving toxicity factors (e.g., an RfD) for PFDA.

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Appendix 3 NHANES Blood Serum Data for PFDA

Serum Perfluorodecanoic acid (PFDA) (1999-2000, 2003-2010)

CAS Number 335-76-2

Geometric mean and selected percentiles of serum concentrations (in µg/L) for the U.S. population from the National Health and Nutrition Examination Survey.

Demographic Categories	Survey (Years)	Geometric Mean (95% CI)	50th Percentile (95% CI)	75th Percentile (95% CI)	90th Percentile (95% CI)	95th Percentile (95% CI)	Sample Size
Total population	99-00	*	<LOD	.200 (<LOD-.300)	.400 (.300-.600)	.600 (.400-1.00)	1432
Total population	03-04	*	<LOD	.300 (<LOD-.500)	.600 (.400-1.10)	.900 (.500-1.80)	2094
Total population	05-06	.355 (.297-.423)	.300 (.300-.400)	.500 (.400-.700)	.900 (.600-1.60)	1.50 (.900-2.60)	2120
Total population	07-08	.286 (.264-.309)	.300 (.300-.300)	.400 (.400-.500)	.700 (.600-.700)	.900 (.800-1.00)	2100
Total population	09-10	.279 (.258-.303)	.300 (.300-.300)	.400 (.400-.500)	.700 (.600-.800)	.900 (.800-1.10)	2233
Age 12-19 years	99-00	*	<LOD	<LOD	.300 (.200-.400)	.400 (.300-.700)	497
Age 12-19 years	03-04	*	<LOD	<LOD	.500 (<LOD-1.00)	.800 (.300-1.20)	640
Age 12-19 years	05-06	.295 (.258-.338)	.300 (.200-.300)	.500 (.400-.500)	.600 (.500-.800)	.800 (.600-1.60)	640
Age 12-19 years	07-08	.231 (.214-.248)	.200 (.200-.300)	.300 (.300-.400)	.500 (.400-.500)	.600 (.500-.700)	357
Age 12-19 years	09-10	.220 (.198-.245)	.200 (.200-.200)	.300 (.300-.300)	.400 (.400-.600)	.600 (.400-.800)	364
Age 20+ years	99-00	*	<LOD	.300 (.200-.300)	.400 (.300-.700)	.600 (.400-1.40)	935
Age 20+ years	03-04	*	<LOD	.400 (<LOD-.500)	.700 (.400-1.00)	.900 (.500-1.80)	1454
Age 20+ years	05-06	.364 (.303-.438)	.300 (.300-.400)	.500 (.400-.700)	1.00 (.600-1.70)	1.50 (.900-2.60)	1480
Age 20+ years	07-08	.295 (.271-.321)	.300 (.300-.300)	.400 (.400-.500)	.700 (.600-.800)	.900 (.800-1.10)	1743
Age 20+ years	09-10	.289 (.265-.314)	.300 (.300-.300)	.400 (.400-.500)	.700 (.600-.800)	.900 (.800-1.20)	1869
Males	99-00	*	<LOD	.300 (.200-.300)	.400 (.300-.700)	.500 (.300-1.90)	684
Males	03-04	*	<LOD	.400 (<LOD-.500)	.800 (.400-1.40)	1.10 (.600-2.10)	1053
Males	05-06	.381 (.318-.456)	.400 (.300-.400)	.600 (.400-.800)	1.00 (.600-2.20)	1.70 (1.00-2.60)	1048
Males	07-08	.306 (.283-.331)	.300 (.300-.300)	.400 (.400-.500)	.700 (.600-.800)	.900 (.800-1.20)	1059
Males	09-10	.289 (.264-.318)	.300 (.300-.300)	.400 (.400-.500)	.600 (.500-.800)	.800 (.600-1.20)	1075
Females	99-00	*	<LOD	.200 (<LOD-.300)	.400 (.300-.600)	.600 (.300-1.40)	748
Females	03-04	*	<LOD	.300 (<LOD-.400)	.500 (.400-.800)	.800 (.500-1.20)	1041
Females	05-06	.331 (.277-.396)	.300 (.300-.400)	.500 (.400-.600)	.900 (.600-1.40)	1.30 (.800-2.30)	1072
Females	07-08	.267 (.245-.292)	.300 (.200-.300)	.400 (.400-.500)	.600 (.500-.800)	.800 (.700-1.10)	1041
Females	09-10	.270 (.248-.295)	.300 (.200-.300)	.400 (.400-.500)	.700 (.600-.800)	1.00 (.800-1.10)	1158
Mexican Americans	99-00	*	<LOD	<LOD	.300 (<LOD-.400)	.300 (<LOD-1.50)	521
Mexican Americans	03-04	*	<LOD	<LOD	.500 (.400-.500)	.600 (.500-.800)	485
Mexican Americans	05-06	.283 (.245-.327)	.300 (.200-.300)	.400 (.300-.500)	.600 (.500-1.00)	1.00 (.500-2.40)	499
Mexican Americans	07-08	.253 (.222-.289)	.200 (.200-.300)	.400 (.300-.500)	.600 (.400-.700)	.600 (.500-1.40)	391
Mexican Americans	09-10	.242 (.215-.272)	.200 (.200-.300)	.400 (.300-.400)	.500 (.500-.600)	.700 (.600-.800)	461
Non-Hispanic Blacks	99-00	*	.200 (<LOD-.300)	.400 (.200-.800)	.800 (.500-1.40)	1.10 (.600-2.30)	269
Non-Hispanic Blacks	03-04	*	<LOD	.400 (<LOD-.700)	.800 (.400-1.50)	1.00 (.500-3.10)	538
Non-Hispanic Blacks	05-06	.405 (.309-.531)	.400 (.300-.500)	.600 (.400-.900)	1.20 (.600-2.90)	2.30 (1.10-3.70)	544
Non-Hispanic Blacks	07-08	.331 (.298-.368)	.300 (.300-.400)	.500 (.400-.600)	.800 (.600-.900)	1.00 (.800-1.50)	419
Non-Hispanic Blacks	09-10	.336 (.298-.379)	.300 (.300-.300)	.500 (.400-.600)	.800 (.600-1.00)	1.10 (.800-2.60)	391
Non-Hispanic Whites	99-00	*	<LOD	.200 (<LOD-.300)	.400 (.300-.500)	.500 (.400-.800)	491
Non-Hispanic Whites	03-04	*	<LOD	.300 (<LOD-.500)	.600 (.400-1.00)	.900 (.500-1.80)	962
Non-Hispanic Whites	05-06	.350 (.294-.417)	.300 (.300-.400)	.500 (.400-.700)	.900 (.600-1.50)	1.40 (.800-2.30)	935
Non-Hispanic Whites	07-08	.276 (.254-.301)	.300 (.200-.300)	.400 (.400-.500)	.600 (.500-.700)	.900 (.700-.900)	931
Non-Hispanic Whites	09-10	.270 (.240-.304)	.300 (.200-.300)	.400 (.300-.500)	.600 (.500-.800)	.800 (.600-1.10)	1031

Limit of detection (LOD, see Data Analysis section) for Survey years 99-00, 03-04, 05-06, 07-08, and 09-10 are 0.2, 0.3, 0.2, 0.2, and 0.1 respectively.

<LOD means less than the limit of detection, which may vary for some chemicals by year and by individual sample.

* Not calculated: proportion of results below limit of detection was too high to provide a valid result.

Biomonitoring Summary: https://www.cdc.gov/biomonitoring/PFAS_BiomonitoringSummary.html
Factsheet: https://www.cdc.gov/biomonitoring/PFAS_FactSheet.html

Serum Perfluorodecanoic acid (PFDA) (2011 - 2018)

CAS Number 335-76-2

Geometric mean and selected percentiles of serum concentrations (in µg/L) for the U.S. population from the National Health and Nutrition Examination Survey.

Demographic Categories	Survey (Years)	Geometric Mean (95% CI)	50th Percentile (95% CI)	75th Percentile (95% CI)	90th Percentile (95% CI)	95th Percentile (95% CI)	Sample Size
Total population	11-12	.199 (.181-.220)	.190 (.170-.210)	.300 (.270-.340)	.480 (.420-.580)	.690 (.600-.770)	1904
Total population	13-14	.185 (.165-.208)	.200 (.200-.200)	.300 (.300-.300)	.500 (.400-.600)	.700 (.600-.900)	2168
Total population	15-16	.154 (.140-.169)	.100 (.100-.200)	.300 (.200-.300)	.400 (.400-.600)	.700 (.500-.900)	1993
Total population	17-18	.193 (.178-.209)	.200 (.200-.200)	.300 (.300-.300)	.400 (.300-.500)	.600 (.500-.900)	1929
Age 12-19 years	11-12	.146 (.126-.168)	.150 (.120-.170)	.200 (.180-.230)	.290 (.240-.340)	.360 (.290-.560)	344
Age 12-19 years	13-14	.136 (.122-.152)	.100 (.100-.200)	.200 (.200-.200)	.300 (.200-.400)	.400 (.300-.500)	402
Age 12-19 years	15-16	*	.100 (<LOD-.100)	.200 (.100-.200)	.200 (.200-.400)	.300 (.200-.500)	353
Age 12-19 years	17-18	.153 (.136-.173)	.200 (.100-.200)	.200 (.200-.300)	.300 (.200-.300)	.400 (.300-.600)	313
Age 20+ years	11-12	.209 (.189-.230)	.200 (.180-.230)	.320 (.280-.370)	.510 (.440-.590)	.730 (.630-.850)	1560
Age 20+ years	13-14	.193 (.171-.218)	.200 (.200-.200)	.300 (.300-.400)	.500 (.400-.600)	.800 (.600-.900)	1766
Age 20+ years	15-16	.160 (.144-.178)	.200 (.100-.200)	.300 (.200-.300)	.400 (.400-.600)	.700 (.500-1.00)	1640
Age 20+ years	17-18	.199 (.183-.216)	.200 (.200-.200)	.300 (.300-.300)	.400 (.300-.600)	.600 (.500-.900)	1616
Males	11-12	.206 (.184-.232)	.200 (.180-.230)	.310 (.260-.370)	.440 (.380-.550)	.620 (.480-.810)	966
Males	13-14	.198 (.175-.225)	.200 (.200-.200)	.300 (.300-.400)	.500 (.400-.700)	.800 (.600-1.00)	1032
Males	15-16	.153 (.137-.172)	.100 (.100-.200)	.300 (.200-.300)	.400 (.300-.600)	.700 (.400-1.00)	964
Males	17-18	.190 (.177-.204)	.200 (.200-.200)	.300 (.200-.300)	.400 (.300-.400)	.500 (.400-.600)	952
Females	11-12	.193 (.177-.211)	.190 (.170-.210)	.290 (.260-.340)	.530 (.410-.640)	.690 (.640-.830)	938
Females	13-14	.174 (.155-.195)	.200 (.100-.200)	.300 (.200-.300)	.500 (.400-.500)	.700 (.500-.900)	1136
Females	15-16	.154 (.141-.168)	.100 (.100-.200)	.200 (.200-.300)	.400 (.400-.600)	.800 (.500-1.10)	1029
Females	17-18	.196 (.176-.219)	.200 (.200-.200)	.300 (.200-.300)	.500 (.400-.600)	.700 (.500-1.10)	977
Mexican Americans	11-12	.176 (.150-.205)	.170 (.150-.200)	.260 (.210-.300)	.380 (.300-.530)	.530 (.360-.600)	211
Mexican Americans	13-14	.145 (.125-.169)	.100 (.100-.200)	.200 (.200-.300)	.300 (.200-.500)	.400 (.300-1.40)	332
Mexican Americans	15-16	.124 (.111-.138)	.100 (<LOD-.100)	.200 (.200-.200)	.300 (.200-.300)	.400 (.300-.800)	370
Mexican Americans	17-18	.162 (.138-.190)	.200 (.100-.200)	.200 (.200-.300)	.300 (.200-.500)	.400 (.300-.800)	297
Non-Hispanic Blacks	11-12	.214 (.193-.237)	.200 (.180-.220)	.330 (.280-.380)	.590 (.420-.850)	.880 (.670-1.06)	485
Non-Hispanic Blacks	13-14	.200 (.162-.246)	.200 (.200-.200)	.300 (.200-.500)	.600 (.400-.900)	.900 (.700-1.20)	455
Non-Hispanic Blacks	15-16	.155 (.140-.171)	.100 (.100-.200)	.300 (.200-.300)	.500 (.400-.500)	.800 (.500-1.10)	439
Non-Hispanic Blacks	17-18	.189 (.162-.220)	.200 (.100-.200)	.300 (.200-.300)	.500 (.400-.700)	.800 (.500-1.10)	430
Non-Hispanic Whites	11-12	.193 (.171-.219)	.190 (.170-.220)	.290 (.260-.340)	.440 (.360-.590)	.620 (.480-.740)	666
Non-Hispanic Whites	13-14	.184 (.158-.213)	.200 (.200-.200)	.300 (.200-.400)	.500 (.400-.500)	.700 (.500-.800)	862
Non-Hispanic Whites	15-16	.150 (.136-.166)	.100 (.100-.200)	.200 (.200-.300)	.400 (.300-.500)	.600 (.400-.700)	619
Non-Hispanic Whites	17-18	.196 (.178-.215)	.200 (.200-.200)	.300 (.200-.300)	.400 (.300-.600)	.600 (.400-.900)	667
All Hispanics	11-12	.182 (.156-.212)	.170 (.150-.200)	.270 (.210-.330)	.430 (.330-.530)	.540 (.440-.760)	406
All Hispanics	13-14	.150 (.135-.167)	.200 (.100-.200)	.200 (.200-.300)	.300 (.300-.400)	.400 (.300-1.00)	537
All Hispanics	15-16	*	.100 (<LOD-.100)	.200 (.200-.300)	.300 (.300-.400)	.500 (.400-.600)	629
All Hispanics	17-18	.176 (.154-.201)	.200 (.200-.200)	.200 (.200-.300)	.300 (.300-.500)	.400 (.300-.600)	473
Asians	11-12	.367 (.308-.438)	.350 (.280-.420)	.670 (.510-.870)	1.35 (.870-2.05)	2.05 (1.19-2.52)	291
Asians	13-14	.360 (.294-.439)	.400 (.300-.500)	.700 (.500-.900)	1.50 (1.00-2.10)	2.20 (1.60-3.30)	236
Asians	15-16	.308 (.254-.373)	.300 (.200-.400)	.700 (.400-.900)	1.30 (.800-1.90)	2.10 (1.00-4.60)	220
Asians	17-18	.278 (.227-.340)	.200 (.200-.300)	.500 (.300-.600)	1.10 (.600-1.20)	1.20 (.900-2.40)	257

Limit of detection (LOD, see Data Analysis section) for Survey years 11-12, 13-14, 15-16, and 17-18 are 0.100, 0.100, 0.100, and 0.100 respectively.

<LOD means less than the limit of detection, which may vary for some chemicals by year and by individual sample.

* Not calculated: proportion of results below limit of detection was too high to provide a valid result.

Biomonitoring Summary: https://www.cdc.gov/biomonitoring/PFAS_BiomonitoringSummary.html
Factsheet: https://www.cdc.gov/biomonitoring/PFAS_FactSheet.html

Serum Perfluorodecanoic acid (PFDA) (Special Sample of Serum PFAS in Children, 2013-2014)

CAS Number 335-76-2

Geometric mean and selected percentiles of serum concentrations (in µg/L) for the U.S. population from the National Health and Nutrition Examination Survey.

Demographic Categories	Survey (Years)	Geometric Mean (95% CI)	50th Percentile (95% CI)	75th Percentile (95% CI)	90th Percentile (95% CI)	95th Percentile (95% CI)	Sample Size
Total population	13-14	*	<LOD	.170 (.130-.230)	.310 (.240-.360)	.370 (.300-.440)	525
Age 3-5 years	13-14	*	<LOD	.170 (.120-.320)	.340 (.160-.470)	.410 (.330-.750)	149
Age 6-11 years	13-14	*	<LOD	.170 (.140-.200)	.290 (.240-.320)	.350 (.320-.380)	376
Males	13-14	*	<LOD	.160 (.120-.230)	.300 (.210-.360)	.360 (.250-.510)	284
Females	13-14	*	.100 (<LOD-.120)	.180 (.150-.230)	.320 (.240-.370)	.380 (.270-.470)	241
All Hispanics	13-14	*	<LOD	.180 (.130-.230)	.270 (.240-.340)	.400 (.270-.470)	186
Other	13-14	*	<LOD	.170 (.120-.240)	.320 (.230-.370)	.370 (.270-.470)	339

Limit of detection (LOD, see Data Analysis section) for Survey year 13-14 is 0.1.

<LOD means less than the limit of detection, which may vary for some chemicals by year and by individual sample.

* Not calculated: proportion of results below limit of detection was too high to provide a valid result.

Biomonitoring Summary: https://www.cdc.gov/biomonitoring/PFAS_BiomonitoringSummary.html
Factsheet: https://www.cdc.gov/biomonitoring/PFAS_FactSheet.html

Reference:

See NHANES Biomonitoring Data Tables at: https://www.cdc.gov/exposurereport/data_tables.html

Appendix 4 Tables of Toxicity Factors for PFDA and Associated Salts and for PFOS and Associated Salts for Input into the Texas Air Monitoring Information System (TAMIS)

Table 6. Chronic Health and Welfare-Based Screening Values for Perfluorodecanoic Acid (PFDA)

Screening Level Type	Duration	(mg/kg-d)	Usage	Flags	Surrogated/ RPF	Critical Effect(s)	Notes
RfD	70 yr	2.0E-07	N	None	--	increased relative liver weight (female rats) in a 28-day oral study	--
$^{chronic}OAEL_{(nc)}$	28 days	7.9E-04	N	None	--	Same as above	--

Usage:
P = Used in Air Permitting
M = Used to Evaluate Air Monitoring Data
R = Used to Calculate Remediation Cleanup Levels
N = Usage Not Defined

Flags:
A = AMCV report
S = ESL Summary Report
D = ESL Detail Report

Table 7. Chronic Health and Welfare-Based Screening Values for Ammonium Perfluorodecanoate

Screening Level Type	Duration	(mg/kg-d)	Usage	Flags	Surrogated/ RPF	Critical Effect(s)	Notes
RfD	70 yr	2.1E-07	N	None	--	increased relative liver weight (female rats) in a 28-day oral study	--
$^{chronic}OAEL_{(nc)}$	28 days	8.2E-04	N	None	--	Same as above	--

Usage:
P = Used in Air Permitting
M = Used to Evaluate Air Monitoring Data
R = Used to Calculate Remediation Cleanup Levels
N = Usage Not Defined

Flags:
A = AMCV report
S = ESL Summary Report
D = ESL Detail Report

Table 8. Chronic Health and Welfare-Based Screening Values for Sodium Perfluorodecanoate

Screening Level Type	Duration	(mg/kg-d)	Usage	Flags	Surrogated/ RPF	Critical Effect(s)	Notes
RfD for PFDA	70 yr	2.1E-07	N	None	--	increased relative liver weight (female rats) in a 28-day oral study	--
$^{chronic}OAEL_{(nc)}$	28 days	8.2E-04	N	None	--	Same as above	--

Usage:
P = Used in Air Permitting
M = Used to Evaluate Air Monitoring Data
R = Used to Calculate Remediation Cleanup Levels
N = Usage Not Defined

Flags:
A = AMCV report
S = ESL Summary Report
D = ESL Detail Report

Table 9. Chronic Health and Welfare-Based Screening Values for Potassium Perfluorodecanoate

Screening Level Type	Duration	(mg/kg-d)	Usage	Flags	Surrogated/ RPF	Critical Effect(s)	Notes
RfD	70 yr	2.1E-07	N	None	--	increased relative liver weight (female rats) in a 28-day oral study	--
$^{chronic}OAEL_{(nc)}$	28 days	8.5E-05	N	None	--	Same as above	--

Usage:
P = Used in Air Permitting
M = Used to Evaluate Air Monitoring Data
R = Used to Calculate Remediation Cleanup Levels
N = Usage Not Defined

Flags:
A = AMCV report
S = ESL Summary Report
D = ESL Detail Report