Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonic Acid (PFOS) and Salts

CAS Registry Numbers:
Perfluorooctanoic acid: 335-67-1
Ammonium perfluorooctanoate: 3825-26-1
Sodium perfluorooctanoate: 335-95-5
Potassium perfluorooctanoate: 2395-00-8
Perfluorooctane sulfonic acid: 1763-23-1
Ammonium perfluorooctanesulfonate: 29081-56-9
Sodium perfluorooctanesulfonate: 4021-47-0
Potassium perfluorooctanesulfonate: 2795-39-3

Prepared by
Joseph T. Haney Jr., M.S.
Janet Petruska Hamilton, Ph.D., D.A.B.T.
Caroline Emery, M.S.
Toxicology, Risk Assessment, and Research Division

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Acronyms and Abbreviations

Acronyms and Abbreviations	Definition
ACGIH	American Conference of Governmental Industrial Hygienists
ADAF	age-dependent default adjustment factor
AEGL	Acute Exposure Guideline Levels
AFFF	aqueous film forming foam
AIC	Akaike information criterion
ALT	alanine aminotransferase
APFO	ammonium perfluorooctanoate
AST	aspartate aminotransferase
ATSDR	Agency for Toxic Substances and Disease Registry
AUC	area under the curve
$^{\circ}$C	degrees Celsius
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
$BMDL_5$	benchmark dose lower confidence limit at a 5% response
$BMDL_{10}$	benchmark dose lower confidence limit at a 10% response
BMDS	benchmark dose software
BMR	benchmark response
bw	body weight
CAR	constitutive androstane receptor
CDC	Centers for Disease Control and Prevention
CL	clearance
CSF	cancer slope factor
d	day(s)
DSD	development support document
eGFR	estimated glomerular filtration rate
EFSA	European Food Safety Authority
ESL	Effects Screening Level

Acronyms and Abbreviations	Definition
^{acute}ESL	acute health-based Effects Screening Level for chemicals meeting minimum database requirements
$^{acute}ESL_{odor}$	acute odor-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
$^{chronic}ESL_{nonthreshold(c)}$	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
FSANZ	Food Standards Australia New Zealand
G	gram
GD	gestation day
GM	geometric mean
GSD	geometric standard deviation
h	hour
HAWC	Health Assessment Workspace Collaborative
HEC	human equivalent concentration
HQ	hazard quotient
HSDB	Hazardous Substance Data Base
IARC	International Agency for Research on Cancer
IgM	immunoglobulin M
IOAEL	inhalation observed adverse effect level
^{acute}IOAEL	acute inhalation observed adverse effect level
$^{chronic}OAEL_{(nc)}$	chronic observed adverse effect level (noncancer effects)
$^{chronic}OAEL_{(c)}$	chronic observed adverse effect level (cancer effects)
IPCS	International Programme on Chemical Safety
IRIS	USEPA Integrated Risk Information System

Acronyms and Abbreviations	Definition
IU/mL	international units per milliliter
kg	kilogram
K_{oc}	organic carbon-water partition coefficient
K_{ow}	n-octanol-water partition coefficient
L	liter
LC_{50}	concentration causing lethality in 50% of test animals
LD_{50}	dose causing lethality in 50% of test animals
LD	lactation day
LOAEL	lowest-observed-adverse-effect-level
$LOAEL_{HED}$	Lowest-observed-adverse-effect-level for human equivalent dose
$LOAEL_{HED\text{-}oral}$	Lowest-observed-adverse-effect-level for human equivalent oral dose
mmHg	A millimeter of mercury; approximately 1 torr, or 1/760 of standard atmospheric pressure
MRL	minimal risk level
MW	molecular weight
µg	microgram
$\mu g/m^3$	micrograms per cubic meter of air
µm	micrometer
mg	milligrams
mg/m^3	milligrams per cubic meter of air
min	minute
mL	milliliter
MMAD	mass median aerodynamic diameter
MOA	mode of action
MOE	margin of exposure
n	number
ng	nanogram
n-PFOA	linear PFOA

Acronyms and Abbreviations	Definition
n-PFOS	linear PFOS
NNDSS	National Notifiable Diseases Surveillance System
NHANES	National Health and Nutrition Examination Survey
NHMRC	Australian Government's National Health and Medical Research Council
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
NRC	National Research Council
OAEL	observed-adverse-effect-level
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PBPK	physiologically based pharmacokinetic
PFAS	Per- and polyfluoroalkyl substances
PFCs	perfluorinated compounds
PFDA	perfluorodecanoic acid
PFHxS	perfluorohexanesulfonic acid
PFNA	perfluorononanoic acid
pH	potential of hydrogen (measure of acidity or alkalinity)
PFOA	perfluorooctanoic acid
PFOS	perfluorooctane sulfonic acid
PND	postnatal day
POD	point of departure
POD_{ADJ}	point of departure adjusted for exposure duration
POD_{HEC}	point of departure adjusted for human equivalent concentration
POD_{HED}	point of departure adjusted for human equivalent dose
$POD_{internal}$	point of departure adjusted for internal dose
PPARα	peroxisome proliferator-activated receptor α
ppb	parts per billion

Acronyms and Abbreviations	Definition
ppm	parts per million
PXR	pregnane X receptor
RDDR	regional deposited dose ratio
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
SFo	oral slope factor
T_3	triiodothyronine
T_4	thyroxine
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
UF_D	incomplete database uncertainty factor
USEPA	United States Environmental Protection Agency

Acronyms and Abbreviations	Definition
V_E	minute volume
WHO	World Health Organization
wk	week(s)
WOE	weight of evidence
yr	year(s)

Chapter 1 Summary Tables

Table 1 and Appendix 7 provide summaries of the health-based inhalation exposure values from an acute evaluation of perfluorooctanoic acid (PFOA) and associated salts for use in air permitting and air monitoring. Table 1 and Appendix 7 provide summaries of the health-based oral exposure values from a chronic evaluation of perfluorooctanoic acid (PFOA) and associated salts for use in TCEQ's remediation program (Texas Risk Reduction Program [TRRP]). Table 2 and Appendix 7 provide summaries of the health-based oral exposure values from a chronic evaluation of perfluorooctane sulfonic acid (PFOS) and associated salts for use in TRRP. Please refer to Section 1.6.2 of the *TCEQ Guidelines to Develop Toxicity Factors* (TCEQ 2015) for an explanation of air monitoring comparison values (AMCVs), reference values (ReVs), and effects screening levels (ESLs) used for review of ambient air monitoring data and air permitting. Refer to Section 1.1.2 of the *TCEQ Guidelines to Develop Toxicity Factors* (TCEQ 2015) for an explanation of how reference doses (RfDs) and oral slope factors (SFo) are used in the calculation of health-protective cleanup levels for the TCEQ's remediation program. Additionally, the tables in Appendix 7 provide inhalation observed effect levels (IOAELs) and observed adverse effect levels (OAELs) following oral exposure. These provide information on levels in air (IOAELs) or oral doses (OAELs) where health effects might be expected to occur in some people. Table 3 and Table 4 provide summary information and the physical/chemical data of PFOA and PFOS, respectively, and the associated salts included in this development support document (DSD).

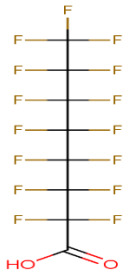
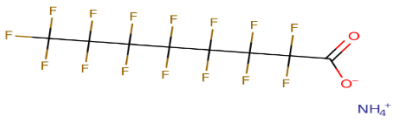
Table 1. Summary of Toxicity Factors for PFOA and Associated Salts

Toxicity Factor	PFOA	Ammonium perfluorooctanoate	Sodium perfluorooctanoate	Potassium perfluorooctanoate	Critical Effect
Acute 1-h inhalation ReV ($\mu g/m^3$)	23	24	24	25	Adverse clinical signs (wet abdomens including the perineal area, chromodacryorrhea and chromorhinorrhea, and unkempt appearance), decreased food consumption, and increased liver weight in pregnant rats
Short-term inhalation ESL ($\mu g/m^3$)	6.8	7.1	7.2	7.4	Same as above
Chronic oral RfD (mg/kg-d)	2.2E-05	2.3E-05	2.3E-05	2.4E-05	Decreased pre-weaning growth in mice
SFo $(mg/kg\text{-}d)^{-1}$	55	53	53	51	Pancreatic acinar cell adenoma and carcinoma in rats

Table 2. Summary of Toxicity Factors for PFOS and Associated Salts

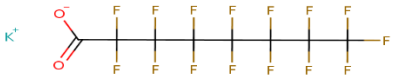
Toxicity Factor	PFOS	Ammonium perfluorooctane sulfonate	Sodium perfluorooctane sulfonate	Potassium perfluorooctane sulfonate	Critical Effect
Chronic oral RfD (mg/kg-d)	2.9E-05	3.0E-05	3.0E-05	3.2E-05	Decreased neonatal weight and weight gain in rats

Table 3. Chemical and Physical Data for Perfluorooctanoic Acid (PFOA) and Salts

Parameter	Perfluorooctanoic acid	Ammonium perfluorooctanoate
Chemical Structure [a]		
Molecular Formula	$C_8HF_{15}O_2$	$C_8H_4F_{15}NO_2$
Molecular Weight	414.07 g/mol	431.101 g/mol
Physical State at 25°C	Solid	Solid
Color	White to off-white [b]	White [c]
Odor	Pungent odor [c]	No data available
CAS Registry Number	335-67-1	3825-26-1
Common Synonym(s)	PFOA; C8; pentadecafluorooctanoic acid; perfluorocaprylic acid; perfluoroheptane carboxylic acid; 2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctanoic acid	APFO; ammonium pentadecafluorooctanoate; ammonium perfluorocaprylate; Fluorad FC 143; PFOA, ammonium salt; azanium, 2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctanoate
Solubility in water [d]	9,500 mg/L	9,500 mg/L
Log K_{ow} [d]	1.76	1.76
Log K_{oc} [d]	2.31	2.31
Vapor Pressure [d]	3.5×10^{-7} mmHg	3.5×10^{-7} mmHg
Density [b]	1.8 g/cm^3	1.8 g/cm^3
Melting Point [b]	54.3 °C	54.3 °C
Boiling Point [b]	188 °C	188 °C

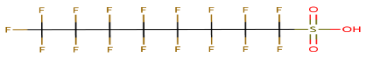
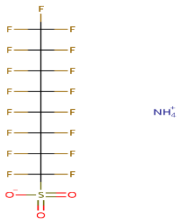
a: CompTox Chemicals Dashboard v2.4.1.
b: ATSDR, 2021 for perfluorooctanoate.
c: PubChem, accessed on July 21, 2023.
d: Texas Risk Reduction Program (TRRP) table for perfluorooctanoic acid.

Table 3. Chemical and Physical Data for Perfluorooctanoic Acid (PFOA) and Salts (cont'd)

Parameter	Sodium perfluorooctanoate	Potassium perfluorooctanoate
Chemical Structure [a]		
Molecular Formula	$C_8F_{15}NaO_2$	$C_8F_{15}KO_2$
Molecular Weight	436.052 g/mol	452.16 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	335-95-5	2395-00-8
Common Synonym(s)	sodium pentadecafluorooctanoate; sodium perfluorocaprylate; sodium 2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctanoate;	potassium perfluorocaprylate; pentadecafluorooctanoic acid potassium salt; potassium,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctanoate;
Solubility in water [b]	9,500 mg/L	9,500 mg/L
Log K_{ow} [b]	1.76	1.76
Log K_{oc} [b]	2.31	2.31
Vapor Pressure [b]	3.5×10^{-7} mmHg	3.5×10^{-7} mmHg
Density [c]	1.8 g/cm^3	1.8 g/cm^3
Melting Point [c]	54.3 °C	54.3 °C
Boiling Point [c]	188 °C	188 °C

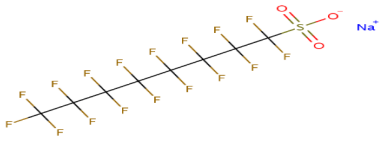
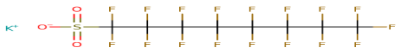
a: CompTox Chemicals Dashboard v2.4.1.
b: TRRP table for perfluorooctanoic acid.
c: ATSDR, 2021 for perfluorooctanoate.

Table 4. Chemical and Physical Data for Perfluorooctane Sulfonic Acid (PFOS) and Salts

Parameter	Perfluorooctane sulfonic acid	Ammonium perfluorooctanesulfonate
Chemical Structure [a]		
Molecular Formula	$C_8HF_{17}O_3S$	$C_8H_4F_{17}NO_3S$
Molecular Weight	500.13 g/mol	517.16 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	1763-23-1	29081-56-9
Common Synonym(s)	PFOS; 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-Heptadecafluoro-1-octanesulfonic acid; heptadecafluoro-1-octanesulfonic acid; Heptadecafluorooctanesulfonic acid; 1-Perfluorooctanesulfonic acid	APFOS; Fluorad FC 93; ammonium heptadecafluorooctanesulfonate; 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-Heptadecafluoro-1-octane sulfonic acid ammonium salt; azanium, 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluorooctane-1-sulfonate
Solubility in water [b]	570 mg/L	570 mg/L
Log K_{ow} [b]	2.45	2.45
Log K_{oc} [b]	3.34	3.34
Vapor Pressure [b]	5.91×10^{-9} mmHg	5.91×10^{-9} mmHg
Density	No data available	No data available
Melting Point [c]	≥ 400 °C	≥ 400 °C
Boiling Point	No data available	No data available

a: CompTox Chemicals Dashboard v2.4.1.
b: TRRP table for perfluorooctane sulfonic acid.
c: ATSDR, 2021 for potassium perfluorooctanesulfonate.

Table 4. Chemical and Physical Data for Perfluorooctane Sulfonic Acid (PFOS) and Salts (cont'd)

Parameter	Sodium perfluorooctanesulfonate	Potassium perfluorooctanesulfonate
Chemical Structure [a]		
Molecular Formula	$C_8F_{17}NaO_3S$	$C_8F_{17}KO_3S$
Molecular Weight	522.11 g/mol	538.22 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	4021-47-0	2795-39-3
Common Synonym(s)	sodium heptadecafluorooctanesulfonate; 1-Octanesulfonic acid, 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-, sodium salt	K-PFOS; potassium heptadecafluorooctane-1-sulfonate; 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-Heptadecafluoro-1-octanesulfonic acid, potassium salt; Fluorad 95; Heptadecafluorooctanesulfonic acid potassium salt
Solubility in water [b]	570 mg/L	570 mg/L
Log K_{ow} [b]	2.45	2.45
Log K_{oc} [b]	3.34	3.34
Vapor Pressure [b]	5.91×10^{-9} mmHg	5.91×10^{-9} mmHg
Density	No data available	No data available
Melting Point [c]	≥ 400 °C	≥ 400 °C
Boiling Point	No data available	No data available

a: CompTox Chemicals Dashboard v2.4.1.
b: TRRP table for perfluorooctane sulfonic acid.
c: ATSDR, 2021 for potassium perfluorooctanesulfonate

Chapter 2 Background Information

2.1 Physical/Chemical Properties

The perfluoroalkyls, PFOA and PFOS 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, PFOA and PFOS are not readily metabolized or degraded, and may accumulate in the human body and persist in the environment. Perfluoroalkyl carboxylates, such as PFOA, and sulfonates, such as PFOS, are resistant to direct photolysis and reaction with acids, bases, oxidants, and reductants. At environmentally and physiologically relevant pHs, PFOA and PFOS and associated salts readily dissociate and will exist in the anion form (i.e., perfluorooctanoate for PFOA, and perfluorooctane sulfonate for PFOS) (ATSDR 2021). For example, ammonium perfluoroocanate (APFO) dissociates to PFOA *in vivo*.

Perfluoroalkyl carboxylates and sulfonates 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 PFOA and PFOS 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. PFOA also has been used as a processing aid in the manufacture of fluoropolymers used as nonstick coatings on cookware. PFOS was previously used as a stain repellant in products including carpets and textiles. PFOA, PFOS, and their precursor substances are no longer produced or

used in the United States or most other industrialized nations; however, these substances are persistent in the environment and exposure near highly contaminated sites may continue to occur (ATSDR 2021).

PFOS and PFOA have been detected in air, water, and soil in and around fluorochemical facilities. However, these industrial releases have been declining since companies began voluntarily phasing out the production and use of PFOA and PFOS in the early 2000s. Nonetheless, due to their resistance to metabolism and degradation, PFOA and PFOS persist and are still found in the environment. Moreover, perfluoroalkyls can also be formed from environmental degradation of precursor compounds released during the manufacture and use of consumer products, including fluorotelomer alcohols such as 8:2 fluorotelomer alcohol in food packaging and air, which can be broken down into PFOA.

The use of AFFF to combat Class B flammable fuel fires may result in PFOA and PFOS contamination as these substances may have been present in AFFF (e.g., legacy AFFF containing PFOS), or in the case of PFOA, may be a contaminant in AFFF or a degradation product of a fluorotelomer present in AFFF. Class B foams are stored and used for fire suppression, fire training, and flammable vapor suppression at military installations and civilian facilities, airports, petroleum refineries and bulk storage facilities, and chemical manufacturing plants. Use of AFFF can result in contamination of soil and water, and PFOA and PFOS can migrate through soil and enter the groundwater. There have been cases where drinking water from private wells near these types of facilities that store and use AFFF have become contaminated with PFOA and/or PFOS.

Other potential sources of PFOA and PFOS contamination are landfills, solid waste, fugitive emissions and releases into air, wastewater treatment plant effluent and sludge, and biosolids that may be used for agricultural application.

PFOA and PFOS have 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. PFOA and PFOS have been detected in the serum of humans. 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 detectable levels of per- and polyfluoroalkyl substances (PFAS) chemicals in their serum. From 1999 to 2018, serum PFOA and PFOS levels declined by more than 70% and more than 85%, respectively. Contaminated drinking water led to increased levels of exposure to PFOA and PFOS for some populations residing near fluoropolymer manufacturing facilities or other PFAS sources (such as military bases), and serum concentrations in these populations may be greater by up to 1 to 2 orders of magnitude

in comparison to the general population (ATSDR 2021, 2022). PFOA and PFOS have 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

A systematic review was conducted to identify inhalation toxicity studies to support development of acute inhalation toxicity factors for PFOA and PFOS (Appendix 1). No relevant data on the acute inhalation toxicity of PFOA or PFOS or associated salts in humans, and no acute inhalation toxicity studies of PFOS or associated salts were identified in the systematic review. For PFOA, three references describing inhalation toxicity studies in animals were identified in the systematic review (Griffith and Long 1980, Staples et al. 1984, Kennedy et al. 1986). These three references include two acute inhalation toxicity studies in rats (Griffith and Long 1980, Kennedy et al. 1986), two short-term inhalation toxicity studies in rats (> 1 day to 28 days, Kennedy et al. 1986), and prenatal and postnatal developmental inhalation toxicity studies in rats (Staples et al. 1984). In these inhalation toxicity studies in rats, the ammonium salt form of PFOA (APFO) was utilized; these studies are described in the following sections.

3.1.1 Acute Inhalation Toxicity Studies

Limited toxicity data on acute exposures to APFO in animals are available. In an acute inhalation study in which 5 male and 5 female ChR-CD albino rats (age not specified, weighing 211-264 g) were exposed for 1 h to a nominal concentration of 18.6 mg/L (18,600 mg/m^3) of APFO, all animals survived to the end of the 14-day post-exposure period (Griffith and Long 1980). Clinical signs during exposure were red nasal discharge, yellow staining of the ano-genital fur, dry rales (e.g., abnormal clicking, crackling, or rattling sounds in the lungs), red material around the eyes, excessive salivation, and lacrimation in most animals. One animal had body tremors. Similar signs were observed during the 14-day post-exposure period, except one animal also had moist rales and there were no body tremors. Animals gained weight during the post-exposure period. In 8/10 rats, bilateral mottling of the lungs was observed, and the discoloration included white, pink, orange, red, tan and brown spots. Two animals had red and/or pink foci on all lobes of the lungs. Pooled serum from male and female rats had measurable organic and inorganic fluoride concentrations; the organic fluoride concentrations indicate systemic exposure to APFO as this is an organic compound. The authors did not report a measured concentration and particle size distribution (i.e., mass median aerodynamic diameter and geometric standard deviation) in this study so it is not known what concentration and fraction of APFO were generated and respirable. Based on the clinical signs and lung gross pathologic findings, the lowest observed adverse effect level (LOAEL) in this study was the nominal concentration of 18,600 mg/m^3.

In another acute inhalation toxicity study (Kennedy et al. 1986), male CRL:CD® BR rats/group (approximately 67 days old, Charles River Breeding Laboratory, Wilmington, MA) were exposed by head-only inhalation to aerosols of APFO for 4 hours in an acute study. Six male rats/group were exposed to mean concentrations of 380, 810, 830, 2200, 4800 or 5700 mg/m^3 APFO. An additional 25 rats/group were exposed to air or 810 mg/m^3 APFO. Five rats/group were sacrificed at 1, 7-, 14-, 27- and 42 days post-exposure and were subjected a gross pathological examination. Histopathological examination of lungs, liver, trachea and the gastrointestinal tract were conducted. Ocular tissues from all rats were stained with fluorescein immediately following cessation of exposure. Clinical observations were performed daily and body weights were obtained twice weekly.

Concentrations of APFO were gravimetrically measured 5 times during the exposure and the time weighted average was calculated. The mass median aerodynamic diameter (MMAD) was determined using a cascade impactor and the results (mean ± standard deviation) were as follows: 380 mg/m^3 (2.4 ± 2.4 µm), 810 mg/m^3 (1.8 ± 2.8 µm), 830 mg/m^3 (1.8 ± 2.5 µm), 2200 mg/m^3 (7.6 ± 3.8 µm), 4800 mg/m^3 (1.6 ± 3.4 µm), and 5700 mg/m^3 (6.4 ± 3.2 µm).

Deaths occurred in all APFO groups within 48 hours of exposure. Deaths occurred in 1/6, 2/6, 1/6, 6/6, 6/6, and 6/6 rats in the 380, 810, 830, 2200, 4800 and 5700 mg/m^3 groups, respectively. At exposure concentrations ≥ 810 mg/m^3, corneal opacity and corrosion were observed, as confirmed by fluorescein staining. During exposure, clinical signs were gasping, irregular breathing, and red discharge around the eyes and nose. Rats that died during the exposure period had hyperinflated lungs. Material that appeared to be the test compound was present in the stomach and foamy white exudate was present in the trachea. Upon gross examination, livers appeared enlarged.

In rats in the 810 mg/m^3 group that were retained for up to 42 days post-exposure, the livers appeared to return to normal size by the end of the 42-day post-exposure period. Following exposure, rats exposed to APFO had pulmonary edema, which was no longer present at 7 days post-exposure. Irritation of the stomach was observed but resolved by 14 days post-exposure. There were no histopathologic findings in the liver. A no observed adverse effect level (NOAEL) was not identified in the acute inhalation study, with mortality occurring at all exposure concentrations (≥ 380 mg/m^3).

The acute inhalation toxicity study in Griffith and Long (1980) is not appropriate for derivation of a toxicity factor because this study had one exposure concentration, did not include a control group, and did not report a measured concentration and particle size distribution (i.e., MMAD and geometric standard deviation [GSD]) so it is not known what concentration and fraction of APFO were generated and respirable. Additionally, given the availability of other inhalation studies in which milder effects were observed, the endpoint of mortality observed in the Kennedy et al. (1986) study also is not appropriate for derivation of an acute ReV and ^{acute}ESL.

As per the TCEQ guidelines (TCEQ 2015) toxicity factors are set to protect the health of the general public and the biological endpoint of choice for derivation of a toxicity factor will generally be a mild effect. Because milder effects were observed in the other available inhalation toxicity studies, the acute studies in which mortality was observed at all exposure concentration will not be used to derive toxicity factors. Therefore, available data on short-term exposures (> 1 day to 28 days) and exposures during prenatal and postnatal development in animals were considered for derivation of the acute ReV and ^{acute}ESL.

3.1.2 Key and Supporting Studies

3.1.2.1 Animal Studies

3.1.2.1.1 Staples et al. (1984) Prenatal and Postnatal Developmental Inhalation Toxicity Studies in Rats – Key Study

Female Sprague Dawley rats (Crl:CD[SD]BR, Charles River Breeding Laboratories, North Wilmington, MA) at approximately 55 days old and weighing 151-198 g were mated to male rats of the same strain and source and of approximately 55 to 85 days of age. Prior to breeding, male and female rats had ophthalmoscopic examinations and rats with eye lesions were excluded from breeding. Mated females were exposed via inhalation in whole body chambers for 6 h/day to aerosols of APFO from gestation day (GD) 6 to GD 15, for a total of 10 exposure days. In the first inhalation study, the aerosol concentrations were 0, 0.1, 1, and 25 mg/m^3; due to severe toxicity observed in rats exposed to 25 mg/m^3, a second inhalation study was performed with aerosol concentrations of 0, 0.1, 1 and 10 mg/m^3. For the teratology portion of the inhalation studies, there were 12 mated females/group, except for the 10 mg/m^3 group which had 15 mated females/group, with additional control groups of 6 dams/group pair-fed to the animals in the 10 and 25 mg/m^3 groups. Specifically, on each day of gestation, the groups of pair-fed controls were given the amount of feed consumed on the same gestation day by rats in the corresponding exposure group (i.e., 10 or 25 mg/m^3; when animals were housed 2 per cage, then their average food consumption for each day was the amount fed to the pair-fed rat. In the first inhalation study, an additional 12 dams/group were allowed to litter for postnatal evaluations of pups. In the second inhalation study an additional 6 dams/group in the control and 10 mg/m^3 groups were allowed to litter for postnatal observations of pups.

Dams were housed 2 per cage for the inhalation study. Dams were weighed prior to breeding and on GDs 1, 6, 9, 13, 16 and 21 for the teratology studies and on GDs 1, 6 and 21 for the dams allowed to litter. Clinical observations were performed at breeding and daily from GD 6-21. Food consumption was measured during gestation for dams assigned to the teratology portion only.

For the teratology portion, dams were sacrificed on GD 21 and were examined macroscopically and liver weights were recorded. Numbers of corpora lutea and implantation sites were counted and numbers of live, dead, and resorbed fetuses were recorded. The uterus of any dams that appeared non-gravid was stained with ammonium sulfide to detect early resorptions. The weight of the intact and empty uterus was recorded. Live and dead fetuses were weighed and sexed, and examined for external alterations. Fetuses were examined for visceral and skeletal alterations and for macroscopic and microscopic alterations of the eyes; eyes were not examined in the 1 and 10 mg/m^3 groups. The examiner was blinded to the study group designation. Pups retained for postnatal observations were examined externally and had ophthalmoscopic examinations performed.

For the postnatal observational portion, dams were weighed and examined for clinical signs on postnatal days (PNDs) 1, 7, 14, and 22. On PND 1, pups from each dam were counted, weighed and examined for external alterations. Pups were weighed and examined for clinical signs on PNDs 4, 7, 14, and 22. An ophthalmologist examined the eyes of pups between PNDs 15 and 17. All pups were sacrificed on PND 35.

The litter was used as the experimental unit for statistical evaluation, and the study authors combined the results of each inhalation study for statistical analysis.

Concentrations of APFO were determined gravimetrically at 0.5 or 1-h intervals depending on the exposure concentration. Additionally, the collected samples (all samples collected for the low exposure concentration and 5-6 samples for all other exposure concentrations) were analyzed spectrophotometrically for APFO concentration. Filter samples collected from the control chamber were also analyzed periodically. The MMAD for the high concentration in each study was determined using a cascade impactor.

Mean achieved gravimetric concentrations were 0, 0.13, 1.1, 10, and 21 mg/m^3 and were similar to concentrations measured using the analytical method (spectrophotometric detection). In both inhalation studies, the MMADs ranged from 1.4 to 3.4 µm at the highest exposure concentration.

Teratology portion of the inhalation studies

During gestation 3 dams died in the 25 mg/m^3 group and of the two examined postmortem, both had resorptions. Clinical signs were observed in dams in the 10 and 25 mg/m^3 groups only and included wet abdomens including the perineal area, chromodacryorrhea[a] and chromorhinorrhea[a], and unkempt appearance. In addition, 4 dams in the 25 mg/m^3 group were lethargic. Significantly lower food consumption was observed on GDs 6 to 15 in the 10 and 25 mg/m^3 groups when compared to the control group but was not different from the pair-fed control groups. Significantly lower body weight gain was seen in the 25 mg/m^3 group only; mean body weight gains from GDs 6 to 15 and from GDs 6 to 21 were 37% and 34% lower, respectively, than that of control. Absolute and relative liver weights in the 25 mg/m^3 group and relative liver weights in the 10 mg/m^3 group were statistically significantly higher than controls.

Mean fetal body weights in the 25 mg/m^3 and corresponding pair-fed groups were both statistically significantly lower than controls; when compared to controls mean fetal body weights were 10% and 12.5% lower than controls in the 25 mg/m^3 and corresponding pair-fed groups, respectively. When compared to the control group, the incidence of partially ossified sternebrae, a skeletal variation, was statistically significantly increased in the 25 mg/m^3 and corresponding pair-fed groups, and was consistent with developmental delay. There were no statistically significant differences from control for malformations.

There were no ophthalmoscopic findings related to APFO. APFO was not teratogenic.

Postnatal observational portion of the inhalation studies

Two dams in the 25 mg/m^3 group died during gestation. Clinical signs were observed during gestation in dams in the 10 and 25 mg/m^3 groups only and were similar to those observed in the teratology study. Although not statistically significantly different from controls, mean body weight gain from GD 6 to 21 in dams in the 25 mg/m^3 group was 13% lower than controls. On PND 1, mean pup body weight in the 25 mg/m^3 group was statistically significantly lower (10%) than controls. There were no ophthalmoscopic findings related to APFO.

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[a] Chromodacryorrhoea refers to a condition characterized by red tears, often taken as a sign of stress or disease. Harderian glands next to the orbits secrete porphyrins, lipids and other compounds. High levels of secretion lead to chromodacryorrhoea. With the condition of chromodacryorrhea, when the red-stained lacrimal fluid (red tears) drains into the nasal cavity via the nasal lacrimal duct, this results in a red-colored nasal discharge and the condition known as chromorhinorrhea. While chromodacryorrhea/chromorhinorrhea may result from infection or inflammation of the Harderian gland, the condition(s) may be a manifestation of generalized stress also. (Mason et al. 2004) Also refer to the National Toxicology Program (NTP). Noneoplastic lesion atlas. Special senses system: Harderian gland – pigment https://ntp.niehs.nih.gov/atlas/nnl/special-senses-system/harderian-gland/Pigment

Based on these studies, the LOAEL for maternal toxicity was 10 mg/m^3 and was based on adverse clinical signs and decreased food consumption during gestation; the dams also had increased absolute and relative liver weights (16.1 g and 5.42%, respectively) versus the corresponding pair-fed group (12.8 g and 4.58%, respectively). The relative liver weights of the dams are expressed as a percent and are the ratio of the liver weight to the corrected GD 21 body weight of the dam (i.e., the body weight of the dam minus the products of conception) multiplied by 100. The NOAEL for maternal toxicity was 1 mg/m^3.

The LOAEL for fetal toxicity was 25 mg/m^3 based on decreased body weights and partially ossified sternebrae, a skeletal variation associated with developmental delay. No APFO-related malformations were seen. The NOAEL for fetal toxicity was 10 mg/m^3.

3.1.2.1.2 Kennedy et al. (1986) Short-term Inhalation Toxicity Studies in Rats – Supporting Studies

Male CRL:CD® BR rats/group (approximately 67 days old, Charles River Breeding Laboratory, Wilmington, MA) were exposed by head-only inhalation to aerosols of APFO for 6 h/day for a total of 10 exposure days in two 12-day studies.

In the first study, 24 male rats/group were exposed to 0, 1, 8, or 84 mg/m^3 APFO for 6 h/day for 5 days, followed by 2 days of non-exposure, and then an additional 5 days for a total of 10 exposure days. Rats were weighed and clinical observations obtained on days of exposure and daily during the post-exposure period, excluding weekends. Ocular examination, including examination with a slit-lamp biomicroscope, was conducted on 10 rats/group on days 5 and 9 of exposure. Blood was collected from the tail vein for hematology and serum chemistry evaluations and urine was collected overnight for urinalysis including microscopic examination of sediment from 5 rats/group immediately after the last exposure and at 14- and 25- days post-exposure. Five rats/group were sacrificed at the end of the last exposure, and at 14, 28 or 42 days after the last exposure. A gross pathological examination was performed, and selected organs (lungs, heart, thymus, spleen, liver, kidneys, and testes) were weighed and preserved, along with ear, skin, trachea, thyroid, adrenal glands, mediastinal tissue, sternebrae with bone marrow, stomach, small and large intestines, epididymides, brain and eyes for microscopic examination.

In the second study, 24 male rats/group were exposed to 0, 1, 8, or 84 mg/m^3 APFO for 6 h/day for 5 days, followed by 2 days of non-exposure, and then an additional 5 days for a total of 10 exposure days. Rats were weighed and clinical observations obtained on days of exposure and daily during the post-exposure period, excluding weekends. Rats were weighed and clinical observations were obtained on days of exposure. Blood was collected from the tail vein for selected serum chemistry evaluations (alkaline phosphatase, glutamic-oxaloacetic transaminase, and glutamic-pyruvic transaminase). Five rats/group were sacrificed at the end of

the last exposure, and at 14, 28, 42, or 84 days (4 rats) after the last exposure. A gross pathological examination was performed, selected organs (lungs, heart, thymus, spleen, liver, kidneys, and testes) were weighed and preserved, along with ear, skin, trachea, thyroid, adrenal glands, mediastinal tissue, sternebrae with bone marrow, stomach, small and large intestines, epididymides, brain and eyes for microscopic examination. A terminal blood sample was collected for determination of blood fluoride and perfluorooctanoic acid.

For the APFO groups, chamber concentrations of APFO were measured at 30-minute intervals using an analytical method with spectrophotometric detection. Mean measured concentrations of APFO were 1, 7.6 (rounded to 8), and 84 mg/m^3. The MMADs were determined using a cascade impactor for the mid- and high-concentration exposures and were 3.8 µm for the 8 mg/m^3 group and 1 to 2 µm for the 84 mg/m^3 group.

Rats in all groups, including the control group, had slight to mild nasal and ocular discharge, which was attributed to the head-only exposures. Two deaths occurred in the 84 mg/m^3 group; one rat with severe weight loss, respiratory distress, and lethargy was sacrificed after the third exposure and one rat died during the fourth exposure. On the fifth day of exposure, mean body weight in the 84 mg/m^3 group was statistically significantly lower than controls (7.4% lower than control) but recovered by 8 days post-exposure. No effects were seen on the cornea of the rats. On the last day of exposure, mean serum alkaline phosphatase was 1.4- and 2.0-fold higher than concurrent control in rats in the 8 and 84 mg/m^3 groups, respectively. At 14 days post-exposure, mean serum alkaline phosphatase was 1.4-fold higher than concurrent control in the 84 mg/m^3 only. At 28 days post-exposure, there were no differences in serum alkaline phosphatase. In all APFO groups, there were no differences in serum glutamic-oxaloacetic transaminase (also known as aspartate aminotransferase) and glutamic-pyruvic transaminase (also known as alanine aminotransferase) at the end of the exposure and during the post-exposure period.

After the last exposure, mean absolute and relative liver weights were 45% to 59% higher than controls in the 8 and 84 mg/m^3 groups. At 14 days post-exposure, mean absolute and relative liver weights were still higher, but to a lesser extent than at the end of exposure; mean absolute liver weights were 19% and 29% higher and mean relative liver weights were 11% and 23% higher in the 8 and 84 mg/m^3, respectively, relative to concurrent control. At 28 days post-exposure, mean absolute liver weights were 16% and 22% higher and mean relative liver weights were 8.3% and 13% higher in the 8 and 84 mg/m^3 groups, respectively, relative to concurrent control. The increase in liver weight correlated with gross findings of enlarged liver. At 42- and 84- days post-exposure, there were no statistically significant differences in liver weights. At the end of exposure, mean relative lung weights were 19% higher and mean relative testes weights were 11% higher in the 84 mg/m^3 group, when compared to concurrent control.

Histopathologic findings were seen in the liver only in the 8 and 84 mg/m^3 groups and included panlobular and centrilobular hepatocellular hypertrophy and necrosis. Panlobular hepatocellular hypertrophy was observed only at the end of the exposure period; in the affected livers entire lobules had uniformly enlarged hepatocytes. Centrilobular hepatocellular hypertrophy was observed at 14- and 28-days post-exposure only. Focal or multifocal hepatocellular necrosis was seen in 2 rats in the 84 mg/m^3 group (one at end of exposure period, one at 14 days post-exposure) in three rats in the 8 mg/m^3 group (one each at end of exposure period, 42- and 84-days post-exposure), and in one control rat at 28 days post-exposure. No liver findings were seen in rats in the 1 mg/m^3 group. All other tissues evaluated were unremarkable upon histopathological examination.

Blood concentrations of APFO were measured at the end of the exposure period and at all post-exposure intervals (14-, 28-, 42-, and 84-days post-exposure) in the control and 84 mg/m^3 groups only; blood concentrations in the 1 and 8 mg/m^3 groups were measured at the end of exposure and at 28 days post-exposure. Blood concentrations of APFO were detected in control animals, but the concentrations were approximately 9- to 12-fold lower than those in the lowest dose group of 1 mg/m^3 at the same sampling intervals. Concentrations of APFO in blood increased with increase in exposure concentration, but the increase was less than dose proportional to the exposure concentration. APFO blood concentrations decreased during the post-exposure period, including in the control rats. At the end of exposure, mean blood concentrations of APFO in the 1, 8 and 84 mg/m^3 groups were 13, 47, and 108 ppm, respectively. At 84-days post-exposure in the 84 mg/m^3 group, the mean blood concentration of APFO was 0.84 ppm, demonstrating a blood half-life of 5-7 days.

A NOAEL of 1 mg/m^3 was identified; the LOAEL was 8 mg/m^3, due to liver findings.

3.1.2.2 Reproductive and Developmental Studies

Reproductive and developmental toxicity data via the inhalation route are limited. The available inhalation reproductive and developmental study is the key study described in Section 3.1.2.1.1.

3.1.3 Metabolism and Mode of Action (MOA) Analysis

Due to the physical and chemical properties of perfluoroalkyl compounds, including PFOA and associated salts such as APFO, these substances are not readily metabolized. PFOA is eliminated slowly, primarily in the urine, and also in feces and breast milk, and bioaccumulates in the body (ATSDR 2021).

A NOAEL of 1 mg/m^3 was identified in a study in male rats exposed 6 h/d for a total of 10 exposure days; the LOAEL was 8 mg/m^3 due to liver findings (increased liver weight, panlobular and centrilobular hepatocellular hypertrophy and necrosis) (Kennedy et al. 1986). The LOAEL

for the increased liver weights in pregnant rats was 10 mg/m^3. The MOA for the increased liver weights and hypertrophy in rats exposed to PFAS has been shown to be activation of the peroxisome proliferator-activated receptor α (PPARα), which may not be relevant to humans (Corton et al. 2014). However, there may be additional MOAs involved in the increases in liver weights in animals exposed to PFOA. Therefore, it is assumed that the liver effects observed in animals may be relevant to humans, although uncertainty remains regarding MOAs other than activation of PPARα in the induction of liver effects due to exposure to PFOA.

The MOAs for the other effects observed following exposure to PFOA (e.g., adverse clinical signs and decreased food consumption during gestation) are unknown but are considered threshold effects.

3.1.4 Health-Based Acute 1-h ReV and ESL

3.1.4.1 Selection of the Key Study, Point of Departure (POD), and Critical Effect

For PFOA (specifically the ammonium salt, APFO) the highest NOAEL was a measured concentration of 1.1 mg/m^3 in pregnant rats exposed for 6 h/d on GDs 6-15 (Staples et al. 1984). The critical effect in pregnant rats was adverse clinical signs (wet abdomens including the perineal area, chromodacryorrhea [red porphyrin secretion from the Harderian glands], and chromorhinorrhea [discharge of a pigmented porphyrin secretion from the nose], and unkempt appearance) decreased food consumption, and increased liver weights during gestation in pregnant rats exposed via inhalation to APFO on GDs 6-15 (Staples et al. 1984). The NOAEL of a measured exposure concentration of 1.1 mg/m^3 was selected as the point of departure (POD) to derive the 1-h ReV.

Although a somewhat lower but similar LOAEL of 8 mg/m^3 for increased liver weights was identified in male rats (Kennedy et al. 1986), this study did not include measurements of MMAD and GSD at the NOAEL of 1 mg/m^3 and, therefore, could not be used for calculation of a regional deposited dose ratio (RDDR). Moreover, the NOAEL in Kennedy et al. (1986) is similar to the NOAEL of 1.1 mg/m^3 identified in the key study in pregnant rats (Staples et al. 1984) and the resulting acute ReV will be protective of adverse effects identified in both studies. The key study in pregnant rats (Staples et al. 1984) did include measurements of MMAD and GSD and was used for calculation of the RDDR.

3.1.4.2 MOA and Dose Metric for Critical Effect

MOA data are not available for the adverse clinical signs and decreased food consumption, but these findings are considered threshold effects and a NOAEL was identified for these effects. Additionally, a MOA of activation of PPARα for increased liver weight was identified, although other MOAs also may be involved. Increased liver weight is also considered a threshold effect

and a NOAEL was identified for this effect. The measured exposure concentration of APFO was used as the dose metric.

3.1.4.3 Adjustments to the POD

3.1.4.3.1 Benchmark Concentration (BMC) Modeling

The incidences of clinical findings and food consumption values at each exposure concentration were not included in the key study publication (Staples et al. 1984); therefore, benchmark concentration modeling could not be performed. Therefore, the NOAEL of 1.1 mg/m^3 was used as the POD for the effects observed.

3.1.4.3.2 Default Exposure Duration Adjustments

Reproductive/developmental studies are usually conducted by exposing animals to repeated exposures/doses over several days (e.g., 6 h/d on GDs 6-15). The TD uses a single day of exposure from the experimental study as the exposure duration (TCEQ 2015). In doing so, the TD recognizes that the reproductive/developmental effects may have been caused by only a single day's exposure that occurred at a critical time during gestation. However, in this case the critical effect is maternal toxicity (i.e., adverse clinical signs, decreased food consumption, increased liver weight), which may have occurred as the result of repeated exposure. In that event, use of a single day of exposure would be considered conservative. The concentration (C_1) at the 6-h exposure duration (T_1) in the key study by Staples et al. (1984) was adjusted to derive an adjusted POD (POD_{ADJ}) concentration (C_2) applicable to a 1-h exposure duration (T_2) using Haber's Rule as modified by ten Berge et al. (1986) ($C_1^n \times T_1 = C_2^n \times T_2$) with n = 3, where both concentration and duration play a role in toxicity.

$POD_{ADJ} = C_2 = [(C_1)^3 \times (T_1 / T_2)]^{1/3} = [(1.1\ mg/m^3)^3 \times (6\ h/1\ h)]^{1/3} = 2.0\ mg/m^3$

3.1.4.3.3 Default Dosimetry Adjustments from Animal-to-Human Exposure

Default dosimetric adjustments for animal-to-human exposure were conducted for the rat study to determine the calculated human equivalent concentration POD (POD_{HEC}) for the critical effect. In the key study, an aerosol of APFO was used. The Applied Research Associates (ARA) Multiple-Path Particle Dosimetry model (MPPD) version 3.04 was used to calculate the deposition fraction of APFO in the target respiratory regions. Parameters necessary for this program include particle diameter, particle density, chemical concentration, and respiratory tract regions considered for deposition.

The MMAD and GSD were measured at the highest exposure concentration of APFO in each study in Staples et al. (1984). As per Table 2 of Staples et al. (1984), particle size distribution data were collected on the first and tenth days of exposure in the first study, which would be GD 6 and 15, respectively, and on the seventh day of exposure for the second study, which

would be GD 12. The data given for MMAD (± GSD) are 1.4 µm (± 4.5) and 2.8 µm (± 6.0) on GDs 6 and 15, respectively, in the first study and 3.4 µm (± 4.3) on GD 12 for the second study. Although MMAD and GSD data were not collected for the 1.1 mg/m^3 group, because the generation system was the same for all exposure concentrations, the particle size distribution should be similar across all exposure concentrations. Therefore, the reported MMAD and GSD data for the high concentration was used for modeling with MPPD software. The MPPD software was unable to model the data with an MMAD (± GSD) of 2.8 µm (± 6.0), or with the average of all MMAD (± GSD) data. However, the MPPD software could model the average of the MMAD (± GSD) of 1.4 µm (± 4.5) and 3.4 µm (± 4.3) resulting in an average of 2.4 µm (± 4.4); therefore, this was used in the calculation of the RDDR.

Because the effects are systemic (increased liver weights, decreased food consumption, adverse clinical observations including effects on the eye and nose), the target region for APFO was considered as the total particle deposition for the entire respiratory tract (i.e., head, tracheobronchial [TB] and pulmonary [P] regions). The density of APFO (Table 3) is 1.8 g/cm^3.

The minute volume (V_E) was calculated based on the body weight of the pregnant rats. Prior to pregnancy the females weighed 151 to 198 g and the average of these two values is 174.5 g. Mean maternal weight gain from gestation days was calculated to be 129.5 g (mean body weight gains for GD 6-15 and 16-21 were 56.7 and 72.8 g, respectively) in the first inhalation study and 116 g in the second inhalation study. However, this weight gain is the gain of the dam as well as the fetuses and other products of conception. In the first study, the weight gain of the dam excluding the products of conception was reported as 56.4 g. So, the weight of the dams on GD 21 (minus the products of conception) was 174.5 + 56.4 g = 230.9 g. Based on equation 4-4 in USEPA guidance (USEPA, 1994; ln [V_E in L/min] = b_0 + b_1 ln [body weight in kg], where ln refers to natural log), a body weight of 230.9 g in rats corresponds to a V_E of 168.4 mL/min.

Of the available rat models, the asymmetric model for the Long-Evans rat was chosen because the current Sprague Dawley asymmetric model has a programming issue (personal communication with Owen Price at Applied Research Associates, Inc). A tidal volume of 1.65 mL and breathing frequency of 102 breaths/min was input into the MPPD software program. For human, using the Yeh Schum symmetric model, a minute volume of 842.74 mL and breathing frequency of 16.38 breaths/min (resulting in a minute volume of 13,800 mL/min), were input into the MPPD software program. All remaining values used were default values in the MPPD program (Appendix 2). Once the total particle distribution was determined, the RDDR was calculated as follows.

$$RDDR = [(V_E)_A / (V_E)_H] \times [DF_A / DF_H] \times [NF_H / NF_A]$$

V_E = minute volume

DF = deposition fraction in the target region(s) of the respiratory tract
NF = normalizing factor (respective body weight)
A = animal
H = human

RDDR = [168.4026 mL/min/ 13,800 mL/min] x [0.3428 / 0.5951] x [70 kg / 0.2309 kg] = 2.13

Then the POD_{HEC} was calculated as follows:

$POD_{HEC} = POD_{ADJ}$ x RDDR = 2.0 mg APFO/m^3 x 2.13 = 4.26 mg APFO/m^3 = 4,260 µg APFO/m^3

3.1.4.4 Adjustments to the POD_{HEC}

The POD_{HEC} based on a NOAEL from the Staples et al. (1984) study was used and UFs were applied to derive the acute 1-h ReV (i.e., assuming a threshold MOA for a noncarcinogenic endpoint). The following UFs were applied to the POD_{HEC} of 4,260 µg/m^3: 10 for intraspecies variability (UF_H), 3 for interspecies variability (UF_A), and 6 for database uncertainty (UF_D).

- A UF_H of 10 was used to account for variation in susceptibility among members of the human population. Human data were insufficient to develop a toxicity factor and so animal data were used to derive the 1-h ReV, and the variability of an acute response in humans is unknown;
- A UF_A of 3 for interspecies uncertainty was used to account for potential toxicodynamic differences between animals and humans, because a default dosimetric adjustment was conducted to account for toxicokinetic differences between animals and humans; and
- A UF_D of 6 was used for database uncertainty. Two acute inhalation studies in rats (Griffith and Long 1980; Kennedy et al. 1986) were performed at very high exposure concentrations that resulted in mortality at all exposure concentrations evaluated (≥ 380 mg/m^3). Two short-term inhalation studies (10 days of exposure each) conducted in male rats at the same exposure concentrations were available (Kennedy et al. 1986). A prenatal/postnatal developmental study conducted via the inhalation route also was available (Staples et al. 1984). Although the database for inhalation exposure in animals is limited, the database for PFOA administered orally is extensive. The systemic effects seen via the inhalation route (i.e., liver findings) were also observed in animals dosed orally. The MOA for the liver effects in rodents (activation of PPARα and other unknown MOAs for this endpoint) would apply to inhalation and oral exposure to PFOA. However, TCEQ has not identified a valid route to route (inhalation route to oral route) physiologically-based pharmacokinetic (PBPK) model. Because uncertainty remains regarding extrapolation from oral to inhalation routes of administration with PFOA, TCEQ will not consider the extensive database for oral toxicity studies in the UF_D for the derivation of the 1-h ReV. A UF_D value of 6 is consistent with the database considerations in Table 4-2 of TCEQ (2015).

$$\text{Acute ReV} = POD_{HEC} / (UF_H \times UF_A \times UF_D)$$

$$= 4{,}260\ \mu g/m^3 / (10 \times 3 \times 6)$$
$$= 4{,}260\ \mu g/m^3 / 180$$
$$= 23.67\ \mu g/m^3$$
$$\mathbf{= 24\ \mu g/m^3}\ \text{(rounded to two significant figures)}$$

3.1.4.5 Health-Based 1-h Acute ReV and ^{acute}ESL

The resulting 1-h acute ReV was rounded to two significant figures at the end of all calculations. The rounded acute ReV was then used to calculate the ^{acute}ESL at the target hazard quotient (HQ) of 0.3 (Table 5).

Table 5. Derivation of the 1-h Acute ReV and ^{acute}ESL for PFOA and Associated Salts

Parameter	Summary
Study	Staples et al. 1984
Study Population	Sprague Dawley pregnant rats, 12-24/group for teratology and 6-18/group for postnatal observations
Study Quality	Medium
Exposure Method	Whole body inhalation to APFO
Exposure Duration	6 h/d on gestation days 6-15, for a total of 10 days of exposure
Critical Effects	Adverse clinical signs (wet abdomens including the perineal area, chromodacryorrhea and chromorhinorrhea, and unkempt appearance), decreased food consumption, and increased liver weight in pregnant rats
NOAEL (POD)	1.1 mg/m^3
LOAEL	10 mg/m^3
POD_{ADJ}	2.0 mg/m^3
POD_{HEC}	4,260 µg/m^3
Total uncertainty factors (UFs)	180
Interspecies UF	10
Intraspecies UF	3
LOAEL-to-NOAEL UF	N/A

Parameter	Summary
Incomplete Database UF *Database Quality*	6 Medium
Acute ReV [1 h] (HQ = 1)	**24 µg/m^3 for APFO** [a]
^{acute}ESL [1 h] (HQ = 0.3)	**7.1 µg/m^3 for APFO** [b]

a: When adjusted for differences in molecular weight, the 1-h ReV is 23 µg/m^3 for perfluorooctanoic acid, 24 µg/m^3 for sodium perfluorooctanoate, and 25 µg/m^3 for potassium perfluorooctanoate.
b: When adjusted for differences in molecular weight, the ^{acute}ESL is 6.8 µg/m^3 for perfluorooctanoic acid, 7.2 µg/m^3 for sodium perfluorooctanoate, and 7.4 µg/m^3 for potassium perfluorooctanoate.

3.1.4.6 Acute Inhalation Observed Adverse Effect Level (IOAEL)

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

The LOAEL of 8 mg/m^3 APFO was identified in the short-term study in male rats exposed for 6 h/d for a total of 10 exposure days and was associated with increased liver weight, and hepatic histopathologic findings of panlobular and centrilobular hepatocellular hypertrophy and necrosis (Kennedy et al. 1986). The LOAEL (10 mg/m^3) from the key study (Staples et al. 1984) used for acute ReV derivation is slightly higher but will be used for IOAEL derivation as well prior to determining the final value (see below). The 6 h/d LOAEL of 8 mg/m^3 APFO observed in the Kennedy et al. (1986) short-term inhalation study in male rats was not adjusted to a 1-h duration because duration adjustments are not conducted for acute IOAELs (TCEQ 2015). Kennedy et al. provided the MMAD at the LOAEL, but not at the NOAEL. An MMAD of 3.8 µm was reported, but a GSD was not reported for the LOAEL of 8 mg/m^3. Because the effects are systemic, the target region for APFO was considered as the total particle deposition for the entire respiratory tract. As described in Section 3.1.4.3.3, MPPD software, version 3.04 was used to calculate the deposition fraction of APFO in the target respiratory regions. With a mean body weight of 266 g during the study (Kennedy et al. 1986), a minute volume of 189 mL was calculated using equation 4-4 in USEPA guidance (USEPA 1994). In the MPPD software, the Long-Evans rat model was chosen because the current Sprague Dawley asymmetric model has a programming issue (personal communication with Owen Price at Applied Research Associates, Inc.). A tidal volume of 1.85 mL and breathing frequency of 102 breaths/min was input into the MPPD software program. For human, using the Yeh Schum symmetric model, a minute volume of 842.74 mL and breathing frequency of 16.38 breaths/min (resulting in a minute volume of 13,800 mL/min), were input into the MPPD software program. All remaining values used were

default values in the MPPD program (Appendix 2). MPPD modeling was performed and the RDDR calculated as follows.

RDDR = [189.1497 mL/min/ 13,800 mL/min] x [0.7191 / 0.9543] x [70 kg / 0.266 kg] = 2.72

Using the RDDR of 2.72 and the LOAEL of 8 mg/m^3 from Kennedy et al. (1986), the acute (i.e., 6-h) IOAEL for APFO would be 22 mg/m^3 (22,000 µg/m^3). If the IOAEL is calculated using the LOAEL of 10 mg/m^3 from Staples et al. (1984) with an RDDR of 2.13, the resultant IOAEL is 21 mg/m^3 (21,000 µg/m^3). TCEQ will use the more conservative **IOAEL of 21,000 µg/m^3** based on the key study of Staples et al. (1984). The margin of exposure between the estimated acute IOAEL of 21,000 µg/m^3 and the 1-h ReV is 875 times for APFO.

3.1.5 Health-Based Acute 24-h ReV

PFOA and PFOS and associated salts are not evaluated in TCEQ ambient air monitoring network (i.e., utilizing a 24-h sampling period); therefore, the TD did not derive a 24-h ReV for these chemicals.

3.2 Welfare-Based Acute Evaluation

3.2.1 Odor Perception

According to PubChem (accessed on July 21, 2023), a pungent odor was reported for PFOA. However, an odor threshold value could not be found for this substance or associated salts. Therefore, an odor-based ESL was not assigned to PFOA and associated salts. No odor data were found for PFOS and associated salts; therefore, an odor-based ESL was not assigned for these chemicals.

3.3 Summary of the Acute Values

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

- Acute 1-h ReV = 23 µg/m^3 for PFOA, 24 µg/m^3 for APFO and sodium perfluorooctanoate, and 25 µg/m^3 for potassium perfluorooctanoate
- ^{acute}ESL [1 h] = 6.8 µg/m^3 for PFOA, 7.1 µg/m^3 for APFO, 7.2 µg/m^3 for sodium perfluorooctanoate, and 7.4 µg/m^3 for potassium perfluorooctanoate

For the evaluation of ambient air monitoring data, the acute 1-h ReV will be used to evaluate 1-h monitoring data. The health-based ^{acute}ESL will be used as the 1-h ESL for air permitting.

The ^{acute}ESL (HQ = 0.3) is not used to evaluate ambient air monitoring data and will be used in air permitting applications.

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

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 PFOA and PFOS (Appendix 1). No animal studies examining adverse effects following chronic inhalation exposure to PFOA have been identified. No animal studies examining effects following any duration of inhalation exposure (e.g., acute, short-term, gestational exposure) to PFOS have been identified. Most of the animal studies available for PFOA and PFOS have been conducted via the oral route of administration. Furthermore, TCEQ has not identified a reliable PBPK model for PFOA or PFOS that could be used for route-to-route extrapolation (i.e., oral to inhalation). Epidemiology studies in workers occupationally exposed to PFOA and PFOS are available; however, these studies do not include air concentration data and instead rely on serum or plasma concentrations of PFOA and PFOS. TCEQ has not identified any PBPK models that could be used for estimation of air concentrations based on serum concentrations of PFOA and PFOS. This precludes the derivation of a chronic ReV. Consequently, the following sections focus exclusively on the oral route of exposure.

4.1.1 PFOA Key and Supporting Studies

4.1.1.1 PFOA Human Studies

Consideration of the weaknesses and limitations of the epidemiological study evidence for PFOA leads TCEQ to conclude that although relevant for hazard identification, the associated epidemiologic results (e.g., immunotoxicity) are not sufficient for quantitative risk assessment and toxicity factor (e.g., RfD) derivation. This is consistent with conclusions of the Australian and New Zealand governments (FSANZ 2021), the Agency for Toxic Substances and Disease Registry (ATSDR; part of the U.S. Department of Health and Human Services), and a number of earlier opinions from national agencies and organizations such as Danish EPA (2016), Expert Health Panel for PFAS (2018), and Kirk et al. (2018). Most recently, the October 2024 Public Consultation Draft for Per- and poly-fluoroalkyl substances (PFAS) by the Australian Government's National Health and Medical Research Council[b] (Australian NHMRC 2024) has concluded in regard to the use of epidemiological studies [*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,

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

> Budtz-Jorgensen and Grandjean 2018, Grandjean et al. 2012, Timmermann 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).

The TCEQ concurs with these conclusions. See Appendix 3 for additional details.

4.1.1.2 PFOA Animal Studies – Oral Route of Administration

To inform the derivation of a chronic oral RfD for PFOA and associated salts, TCEQ used information from multiple sources. TCEQ conducted a systematic review to identify and evaluate animal studies with oral exposure to PFOA (see Appendix 1 and TCEQ's PFAS Systematic Review [TCEQ 2025]). In addition, TCEQ reviewed assessments conducted by other state, federal, or international agencies that derived toxicity factors for PFOA. Part of the toxicity factor derivation process under the TCEQ (2015) guidelines involves consideration of adopting an existing assessment by another agency, with a critical criterion being whether the assessment is sufficiently consistent with how the TCEQ would conduct such an assessment. With this in mind, the TCEQ may adopt all or part of another agency's assessment.

One recently available assessment for PFOA is the draft developed by the Australian NHMRC (2024), which is discussed below in Section 4.1.2 Selection of the Key Study and Critical Effect for PFOA. TCEQ also used information from the USEPA Human Health Toxicity Assessment for PFOA and Related Salts (USEPA 2024a). Both agencies conducted a search of the available literature on PFOA. USEPA's systematic review is described in Chapter 2 of USEPA (2024a). For the Australian NHMRC (2024) assessment, Section 3 of *Evidence Evaluations for Australian Drinking Water Guidelines Chemical Fact Sheets – PFOS, PFHxS, PFOA, PFBS, and GenX Chemicals, Technical Report*[c] summarizes the methods for evidence evaluation review conducted for five PFAS, including PFOA. Section 3 of that technical report provides sufficient

[c] October 17, 2024; available at: https://www.nhmrc.gov.au/health-advice/environmental-health/water/PFAS-review/guideline-development#block-views-block-file-attachments-content-block-1

detail for a third party to reproduce the search. Figure 3-1 of that section shows the overview of the literature search process followed, presented as a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram that describes the study selection process and numbers of records at each stage of screening (Moher et al. 2009). In USEPA's and the Australian NHMRC's assessments, the animal studies identified were consistent with those identified by TCEQ's systematic review.

As discussed in the subsequent sections, the key study that TCEQ ultimately selected for PFOA is Lau et al. (2006) and the critical effect is decreased pre-weaning growth in CD-1 mouse pups exposed to PFOA during gestation and lactation.

4.1.1.3 PFOA Reproductive and Developmental Studies – Oral Route of Administration

Visual data summaries for PFOA-induced developmental and reproductive effects observed in laboratory animal studies were obtained from USEPA (2024a) via HAWC (**https://hawc.epa.gov/summary/assessment/100500248/visuals/**) and are presented in Appendix 5. Results of these studies will be discussed briefly in Section 4.1.1.3.1. and Section 4.1.2. These exposure response arrays helped to compare the LOAELs across various reproductive and developmental studies conducted in animals administered PFOA or associated salts.

4.1.1.3.1. Lau et al. (2006) Oral Prenatal and Postnatal Developmental Toxicity Study in Mice – Key Study

This study was conducted to evaluate the effects of *in utero* exposure to PFOA on prenatal and postnatal development of offspring. Groups of pregnant CD-1 mice (9-45/group, Charles River Laboratories, Raleigh, NC) were administered APFO formulated in deionized water via oral gavage at doses of 0 (water only), 1, 3, 5, 10, 20, or 40 mg/kg-d on GD 1-17. APFO is metabolized to PFOA. Some mice were sacrificed on GD 18 for teratological evaluation of fetuses; one half of each litter was prepared for skeletal evaluation and the other half was prepared for visceral evaluation. The remaining pregnant mice were dosed on GD 18 and allowed to deliver pups. Eye opening was monitored in the pups, and all pups were weaned on PND 23 and separated by sex. The age at which the offspring reached puberty was determined by monitoring vaginal opening in females and preputial separation in males beginning on PND 24. Following achievement of vaginal patency, the age at first detectable estrus was determined by daily evaluation of vaginal cytology.

Decreased maternal weight gain and/or weight loss occurred in dams at doses of 20 and 40 mg/kg-d; loss of all pregnancies occurred at 40 mg/kg-d. In the 20 mg/kg-d group, significant prenatal loss, decreased live fetuses, and decreased fetal weight were observed. On GD 18, maternal liver weights were increased at all doses; however, the increase was non-monotonic at 20 and 40 mg/kg-d due to decreased body weight gain or body weight loss in the dams. In

the 10 and/or 20 mg/kg-d groups, enlarged fontanel and reduced ossification of sternebrae, caudal vertebrae, metacarpals, metatarsals, phalanges, calvaria, supraoccipital, and hyoid were seen; these findings are typically seen with developmental delay. Microcardia was seen in the 10 and 20 mg/kg-d groups, and tail and/or limb defects were observed at dose ≥ 5 mg/kg-d. There was increased time to parturition in the 3, 10, and 20 mg/kg-d groups, but not in the 5 mg/kg-d group. Increased full litter resorptions were observed at doses ≥ 5 mg/kg-d.

Decreased neonatal survival occurred at doses ≥ 5 mg/kg-d; most pups in the 10 and 20 mg/kg-d groups did not survive past the first day of life. Decreased pup weight and growth during pre-weaning occurred at doses ≥ 3 mg/kg-d. Delayed eye opening was seen at doses ≥ 5 mg/kg-d, and delayed vaginal opening and time to first estrus occurred in the 20 mg/kg-d group. There appeared to be a shorter time to preputial separation in all APFO groups despite decreased body weights relative to controls, but the response was non-monotonic at 20 mg/kg-d.

The LOAEL and NOAEL for maternal toxicity were 10 and 5 mg/kg-d, respectively, due to decreased maternal weight gain or weight loss. The LOAEL and NOAEL for fetal/neonatal toxicity were 3 and 1 mg/kg-d, respectively, due to decreased preweaning body weight and growth.

4.1.2 Selection of the Key Study and Critical Effect for PFOA

Because of the large number of PFOA animal studies, TCEQ used summary information from the Australian NHMRC (2024)[d] to focus on studies that were most likely to be candidate key studies. NHMRC (2024) evaluated ten health-based guidance values for PFOA from international jurisdictions for potential adoption or adaptation. Seven guidance values used data in the RfD derivation that had previously not been considered and evaluated by the Australian and New Zealand governments (FSANZ 2017b). However, based on a critical evaluation of the underlying studies, NHMRC (2024) concluded that confidence in the candidate PFOA RfD and guideline values was very low to low. Consequently, the information was not deemed of high enough quality to warrant revision of the current Australian PFOA RfD (and water guideline value) for which the confidence is high. NHMRC (2024) therefore concluded the current Australian guidance value for PFOA of 160 ng/kg-d is still appropriate. See Table 9-1 of NHMRC (2024) for details on the derivation of this health-based guidance value (i.e., RfD), which was based on decreased pre-weaning growth rate, a developmental effect, in pups exposed prenatally to PFOA (GD 1-18) in the Lau et al. (2006) mouse gavage study.

[d] Available at: https://consultations.nhmrc.gov.au/environmental-health/australian-drinking-water-guidelines-2024-pfas/

In addition, an NHMRC *Addendum to PFAS Evidence Evaluation for Australian Drinking Water Guidelines Chemical Fact Sheets* to the 2024 PFAS Review[e] considered the USEPA April 2024 health effects documentation for PFOA (USEPA 2024a) as well as a recently published peer-reviewed scientific paper by an international collaboration of scientists deriving guidance values for PFOA (Burgoon et al. 2023).[f] In this NHMRC Addendum (2024), five draft RfDs (NOAEL- and BMDL-based) are derived based on five additional studies, with confidence ranging from high to low:

- high confidence draft RfD based on NTP (2020, revised 2023)
- medium confidence draft RfD based on Butenhoff et al. (2012a)
- medium confidence draft RfD based on Dewitt et al. (2008)
- low confidence draft RfD based on Abbott et al. (2007)[g]
- low confidence draft RfD based on Song et al. (2018)[h]

Only the high and medium confidence values are discussed herein. Additionally, the 6-month toxicity study in male cynomolgus monkeys (Butenhoff et al. 2002) is discussed here. Note that TCEQ used the internal dose values and human clearance values that are in USEPA (2024a) in the derivation of an RfD. The candidate key studies along with LOAELs and $LOAELs_{HED\text{-}oral}$ are shown in Table 6. TCEQ identifies the critical effects based on comparison of $LOAEL_{HED}$ values (based on human equivalent dose-response effect levels), not based on comparison of values that include uncertainty factors. TCEQ's method is consistent with the definition of critical effect (TCEQ 2015)[i], because greater uncertainty can overcome greater observed sensitivity of

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[e] Available at: https://consultations.nhmrc.gov.au/environmental-health/australian-drinking-water-guidelines-2024-pfas/supporting_documents/SLR%202024%20Addendum%20to%20the%20Evidence%20Evaluation%20%20PFAS%20Evidence%20Review.pdf

[f] This resulted in the critical review of an additional 19 studies for PFOA and/or PFOS.

[g] While this is a mouse developmental study with a relatively low LOAEL for PFOA (0.6 mg/kg-d for decreased pup survival), it is a low confidence study per both USEPA (2024a) and Australia (*Addendum to PFAS Evidence Evaluation for Australian Drinking Water Guidelines Chemical Fact Sheets*). Even so, the PFOA RfD derived by TCEQ (2.2E-05 mg/kg-d) provides a sufficient MOE considering results from this low confidence study (i.e., LOAEL of 17.4 mg/L serum (Table 3 of Abbott et al. 2007, using highest serum concentration based on females with no pups at weaning) × human clearance of 0.00012 L/kg-d (USEPA 2024a, Table 4-6) = $LOAEL_{HED}$ of 0.002 mg/kg-d, which when divided by the RfD provides an MOE of 95).

[h] Australia (*Addendum to PFAS Evidence Evaluation for Australian Drinking Water Guidelines Chemical Fact Sheets*) notes that this PFOA study: did not follow standardized protocols for developmental toxicity experiments; the reported serum PFOA concentration in the paper is unreliable; statistical analysis of the various endpoints did not include the litter in the model to guard against an inflated Type I error rate; thus, Song et al. (2018) and the associated candidate RfD in USEPA (2024a) were rated as of low confidence. Regardless, the PFOA RfD derived by the TCEQ (2.2E-05 mg/kg-d) provides a sufficient MOE considering results from this low confidence PFOA study (i.e., $BMD_{0.5\,SD}$ of 27.5 mg/L serum concentration (Table E-91 of USEPA 2024a) × clearance of 0.00012 L/kg-d (USEPA 2024a) = BMD_{HED} of 0.0033 mg/kg-d, which when divided by the RfD provides an MOE of 150).

[i] The critical effect is basically the first adverse effect as the dose rate increases, which is commonly documented in a study as the study- and endpoint-specific LOAEL and/or an overall study LOAEL. The first adverse effect that may be expected to occur in humans as the dose rate increases can be determined on the basis of comparing $LOAEL_{HED}$ values (TCEQ 2015).

an endpoint, potentially resulting in the selection of the most uncertain endpoint as the critical effect.

Table 6. Candidate key studies, adverse effects, LOAELs, and $LOAELs_{HED\text{-}oral}$ for PFOA

Study	Species	Dosing Duration	Adverse effect	LOAEL (mg/kg-d)	Internal dose	$LOAEL_{HED\text{-}oral}$ [a] (mg/kg-d)
Developmental study (Lau et al. 2006)	CD-1 Mice	GD 1-18	Decreased preweaning growth in pups	3	26.6 mg/L [b]	3.2E-03
Chronic toxicity study (Butenhoff et al. 2012)	Sprague Dawley rats	2 years	Increased serum levels of ALT and AST in males	1.3	43,263.7 mg × d/L [c]	7.6E-03 [d]
Chronic toxicity study (NTP 2020, revised 2023)	Sprague Dawley rats	Perinatal/ postweaning for total of 107 weeks	Liver histopathology (hepatocellular necrosis) in males	1	72.6 mg/L [e]	8.7E-03
Immunotoxicity study (DeWitt et al. 2008)	C57BL/6N mice	15 days	decreased serum sheep red blood cell-specific IgM antibody titers and decreased absolute and relative spleen weights in females	3.75	73.1 mg/L [f]	8.8E-03
Chronic toxicity study (Butenhoff et al. 2002)	Cynomolgus monkeys	Up to 182 days (6 months)	Increased absolute and relative liver weight	3	77 mg/L [g]	9.2E-03
Chronic toxicity study (Butenhoff et al. 2012)	Sprague Dawley rats	2 years	Liver histopathology (cystoid degeneration, hepatocellular hypertrophy, portal mononuclear cell infiltrate) in males	14.2	167,102.5 mg × d/L [c]	2.9E-02 [d]

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GD, gestation day; IgM, immunoglobulin M; LOAEL, lowest-observed-adverse-effect-level; $LOAEL_{HED\text{-}oral}$, lowest-observed-adverse-effect-level human equivalent oral dose
a: calculated using a human clearance of 0.00012 L/kg-d (Table 4-6 in USEPA 2024a)
b: Value from Table E-57 in USEPA 2024a
c: Value from Table E-48 in USEPA 2024a

d: back-calculated conversion factor of 1.75E-07 L/kg-d based on Table 4-13 of USEPA 2024a as equal to the Butenhoff et al. (2012) POD_{HED} of 4.75E-03 mg/kg-d / $POD_{Internal}$ of 27,089.3 mg × d/L. That is, Table 4-13 provides the $POD_{Internal}$ of 27,089.3 mg × d/L and the POD_{HED} of 4.75E-03 mg/kg-d, and the above equation solves for the multiplicative factor to convert the $POD_{Internal}$ of 27,089.3 mg × d/L to the POD_{HED} of 4.75E-03 mg/kg-d.
e: Value from Table E-70 in USEPA 2024a
f: Value from Table E-52 in USEPA 2024a
g: Value from p. 250 of Butenhoff et al. 2002

The high confidence candidate RfD was based on hepatocellular necrosis in the NTP (2020, revised 2023) 2-year rat study. However, the Addendum (NHMRC 2024) indicates that the human relevancy of the hepatic necrosis effect observed in rodents in the NTP (2020, revised 2023) study is uncertain (p. 83 of the 2024 Addendum) given: (1) relevant negative findings in monkey studies (Goldenthal et al. 1978 [j], Butenhoff et al. 2002); and (2) the lack of treatment-related changes in serum levels of liver enzymes in a Phase 1 trial conducted with APFO (APFO dissociates to PFOA) for potential use as a therapeutic agent in cancer patients dosed weekly for up to six weeks at 50-1200 mg APFO (Convertino et al. 2018), resulting in circulating levels of PFOA of more than four orders of magnitude higher than those measured in epidemiological studies (i.e., 3.7-633 mg/L).

Because monkeys are more physiologically similar to humans than rodents, TCEQ also considered the results of the two toxicity studies conducted in non-human primates (cynomolgus monkeys and rhesus monkeys) for derivation of an RfD. Note that in the 6-month study in male cynomolgus monkeys (Butenhoff et al. 2002), animals were administered APFO via capsule at doses of 3, 10, or 30/20 mg/kg-d, resulting in mean steady state serum concentrations of PFOA of 77, 86, and 158 mg/L, respectively. In this 6-month study, monkeys in the high-dose group (30/20 mg/kg-d) initially were administered 30 mg/kg-d; however, this dose was not tolerated due to decreased food consumption and resultant body weight loss during the first week of dosing. Therefore, monkeys in the high-dose group were not dosed on days 12 to 21, and then on day 22 began receiving 20 mg/kg-d APFO. One monkey in the high-dose group was sacrificed in moribund condition and had gastrointestinal findings consistent with dosing injury (although not stated in the publication, the capsules likely were administered via a gavage tube), liver histopathologic findings (midzonal and centrilobular hepatocellular degeneration and necrosis; diffuse hepatocellular vacuolation; hepatocyte basophilia in centrilobular areas), and marked elevations of serum enzymes (> 10-fold increase in ALT, AST, sorbitol dehydrogenase and creatine kinase). Another high-dose monkey had an approximate 10-fold increase in serum ALT, AST and creatine kinase and a 5-fold increase in sorbitol dehydrogenase, but did not have histopathologic findings in the liver. No other monkeys in this study had elevated serum levels of liver enzymes or histopathologic findings in the liver. At the end of the study, liver weights in all APFO dose groups were statistically significantly greater

[j] This reference refers to a technical report of a 90-day study in rhesus monkeys, which was not publicly available, and is cited in USEPA (2024a). The Griffith and Long (1980) publication did include results from this 90-day study in rhesus monkeys.

than control values. No liver findings were reported in the 90-day study in rhesus monkeys (Griffith and Long 1980).

In the Butenhoff et al. (2012a) 2-year study in SD rats, at various intervals throughout the study when compared to concurrent control values, males fed 30 ppm APFO in the diet (dose of 1.3 mg/kg-d) had increased mean serum levels of ALT (up to 2.3-fold) and AST (up to 1.9-fold), but did not have liver histopathologic findings. Males fed APFO at the next highest dietary concentration of 300 ppm in the diet (dose of 14.2 mg/kg-d) had increased mean serum levels of ALT (up to 3.2-fold) and AST (up to 1.8-fold) when compared to concurrent control values, and also had microscopic evidence of hepatotoxicity. Overall, the LOAEL was 1.3 mg/kg-d in male rats due to increases in serum levels of liver enzymes.

For the DeWitt et al. (2008) 15-day mouse immunotoxicity study, the NOAEL and LOAEL for decreased serum sheep red blood cell-specific IgM antibody titers and decreased absolute and relative spleen weights in female C57BL/6N mice were 1.88 and 3.75 mg/kg-d, respectively.

The lowest $LOAEL_{HED\text{-}oral}$ of 3.2E-03 mg/kg-d was identified in the developmental toxicity study in CD-1 mice and the critical effect was decreased preweaning growth rate (Lau et al. 2006), which also is the basis for the current Australian RfD (see Table 23 of FSANZ 2017b). The $LOAELs_{HED\text{-}oral}$ for hepatic effects in the high confidence (NTP 2020, revised 2023) and the medium confidence (Butenhoff et al. 2012) chronic toxicity studies in rats are at least 2.4-fold higher than the $LOAEL_{HED\text{-}oral}$ from Lau et al. (2006). In addition, given the uncertain relevance to humans, the hepatic effects based on the chronic toxicity studies in rats were not identified by TCEQ as the critical effect for derivation of the TCEQ RfD for PFOA. Moreover, the $LOAEL_{HED\text{-}oral}$, based on increased absolute and relative liver weights at all doses in the chronic toxicity study in male cynomolgus monkeys, is 2.9-fold higher than the $LOAEL_{HED\text{-}oral}$ from Lau et al. (2006).

For the DeWitt et al. (2008) 15-day immunotoxicity study in mice, the $LOAEL_{HED\text{-}oral}$ is 2.7-fold higher than the $LOAEL_{HED\text{-}oral}$ for the critical effect.

Based on the above discussions, the NTP (2020, revised 2023) 2-year study in rats, DeWitt et al. (2008) 15-day immunotoxicity study in mice, Butenhoff et al. (2012a) 2-year study in rats, as well as the Butenhoff et al. (2002) 6-month study in cynomolgus monkeys are not considered further herein for RfD development.

Moreover, based on laboratory animal data for PFOA-induced developmental and reproductive endpoints summarized by USEPA (2024a; https://hawc.epa.gov/summary/assessment/100500248/visuals/, see Appendix 5 of this document), an RfD derived based on a mouse POD of 1 mg/kg-d (NOAEL with an associated LOAEL of 3 mg/kg-d; p. 63 of FSANZ 2017b) from the Lau et al. (2006) developmental toxicity study in mice would also be expected to be protective of other developmental effects and

reproductive endpoints, given the margin of exposure (MOE). For example, see footnotes "g" and "h" regarding developmental effect levels in the Abbott et al. (2007) and Song et al. (2018) studies, respectively. Additionally, while reproductive effect levels in rodent (i.e., mouse, rat) studies appear to range from 1-20 mg/kg-d, with the low end of the range coming from the low confidence Song et al. (2018) mouse study (see Appendix 5.2 PFOA Reproductive Endpoints), these lower reproductive effect levels (e.g., 1 mg/kg-d) do not necessarily have a monotonic dose-response, rise to the level of adversity, or otherwise represent endpoints for which a candidate RfD can be derived with sufficient confidence (e.g., USEPA 2024a did not derive candidate RfDs for such effects).[k]

Therefore, TCEQ selected decreased pre-weaning growth rate in pups as the most sensitive effect identified as per TCEQ (2015) guidelines (i.e., comparing $LOAEL_{HED}$ values) of the candidate endpoints considered suitable for candidate RfD derivation in the 2024 Addendum based on: Lau et al. (2006), NTP (2020, revised 2023), DeWitt et al. (2008), and Butenhoff et al. (2012a), as well as Butenhoff et al. (2002). TCEQ's systematic review of the relevant literature for PFOA did not identify any other candidate key studies that were not included in the NHMRC (2024) evaluation.

The average serum concentration of PFOA associated with the NOAEL of 1 mg/kg-d in mice from Lau et al. (2006) was modeled to account for exposure during gestation and lactation, and was reported in USEPA (2024a, Table E-57) to be 15.8 mg/L. The corresponding $POD_{HED\text{-}oral}$ for PFOA was calculated to be 0.0019 mg/kg-d (more details provided in Section 4.1.4.1). Note that USEPA and TCEQ attempted to model the PND 23 pup weight data in benchmark dose software (BMDS) with a benchmark response (BMR) of 5% for neonatal weight, but no models had adequate fit for constant and nonconstant variance. Therefore, the NOAEL approach will be used to derive an RfD.

Accordingly, TCEQ identified the critical effect and derived the TCEQ-calculated $POD_{HED\text{-}oral}$ of 0.0019 mg/kg-d (using PBPK values from USEPA 2024a) corresponding to the NOAEL of 1 mg/kg-d for a developmental effect (i.e., decreased pre-weaning growth rate in pups) based on Lau et al. (2006, NHMRC 2024, FSANZ 2017b) for derivation of the TCEQ's RfD for PFOA. This is consistent with TCEQ's consideration of NHMRC 2024/FSANZ 2017 under the TCEQ toxicity factor guidelines (TCEQ 2015), other animal data for various effects (e.g., developmental,

[k] For example, the effect on serum testosterone levels on PND 70 and testicular index (testis weight / body weight × 100) on PND 70 in the low confidence Song et al. (2018) study were non-monotonic (Tables 4 and 5 of study) and USEPA (2024a) notes that neither the subchronic nor the chronic study in male rats that measured serum testosterone reported decreases across multiple time points ranging from 1 to 21 months (Perkins et al. 2004, Biegel et al. 2001). Effects on the number of Leydig cells on PND 21 and 70, and testicular index (testis weight / body weight x 100) on PND 21 (also associated with a non-monotonic dose-response), in the low confidence Song et al. (2018) study occurred at somewhat higher PFOA doses (≥ 2.5 mg/kg-d; Table 3 and Figure 1 of study), similar to the LOAEL from Lau et al. (2006) for which the associated NOAEL was used by TCEQ for RfD derivation.

reproductive), as well as the agency's determination that the available epidemiological data are unsuitable for quantitative dose-response assessment and toxicity factor derivation (e.g., issues of confounding co-exposures and biological significance/adversity; see Appendix 3), which is consistent with relatively recent evaluations by other agencies (e.g., FSANZ 2021, ATSDR 2021, Australian NHMRC 2024).

4.1.3 MOA Analysis and Dose Metric for PFOA

See USEPA (2024a) for additional discussions of the MOA data relevant to PFOA-induced developmental effects. Briefly, evidence from mechanistic studies that relates to observed developmental effects of PFOA is limited. Several studies in rodents show decreased fetal and pup weight with gestational and lactational exposure to PFOA. Mice appear to be more sensitive than rats to developmental toxicity associated with PFOA. The fetal body weight effects in mice and rats occur at doses that do not produce maternal body weight changes or other apparent maternal effects and therefore are not considered to be due to maternal toxicity. The effects on body weights and growth in pre-weaned pups is a threshold effect, and the key study (Lau et al. 2006) identified a NOAEL and LOAEL for decreased growth in pups prior to weaning.

The dose metric is the internal dose of PFOA from USEPA (2024a, refer to Section E.2.3.4 and Table E-57). Because the critical effect of decreased preweaning growth rate from Lau et al. (2006) is a developmental effect and the pups were exposed during gestation and lactation, the internal dose represents the average concentration normalized per day during these relevant exposure windows in the study (i.e., gestation and lactation). The PBPK model used to calculate the internal dose (Wambaugh 2013) is described further in Section 4.1.3.1.3 of USEPA (2024a).

4.1.4 Adjustments to the POD for PFOA

4.1.4.1 Dosimetry Adjustments from Animal-to-Human Exposure and Serum-to-Oral Dose for PFOA

As mentioned in Section 4.1.2, following a systematic review conducted by TCEQ, as well as review of summary information in support of chronic RfDs developed by other agencies (NHMRC 2024, FSANZ 2017b, USEPA 2024a), TCEQ identified the same critical effect that Australia used in the development of their chronic RfD (NHMRC 2024, FSANZ 2017b). TCEQ calculated a $POD_{HED\text{-}oral}$ of 0.0019 mg/kg-d using toxicokinetic values from USEPA (2024a), corresponding to the NOAEL (1 mg/kg-d) for a developmental effect in mice (i.e., decreased pre-weaning growth rate in pups) based on Lau et al. (2006) for derivation of the TCEQ's RfD for PFOA. Because this POD is based on the average serum concentration associated with the NOAEL (15.8 mg/L, refer to Table E-57 of USEPA 2024a) as the internal dose metric, derivation of an oral RfD expressed as mg/kg-d required extrapolation from a serum concentration

($POD_{HED\text{-}serum}$) to human oral dose ($POD_{HED\text{-}oral}$) using a human clearance value (CL) of 0.00012 L/kg-d (Table 4-6 in USEPA 2024a).

Briefly, the $POD_{HED\text{-}oral}$ for Lau et al. (2006) was based on the average serum concentration derived from the predicted area under the curve (AUC) over the duration of dosing using the USEPA PK model and parameters (Wambaugh et al. 2013, refer to Section 4.1.3.1.3 of USEPA 2024a). Accordingly, the equation for calculation of the $POD_{HED\text{-}oral}$ was:

$POD_{HED\text{-}oral}$ = average serum concentration x CL (in human)

where CL (in human) = 0.00012 L/kg-d for PFOA (section 4.1.3.2 in USEPA 2024a)

Thus, the $POD_{HED\text{-}oral}$ = 15.8 mg/L ($POD_{HED\text{-}serum}$) × 0.00012 L/kg-d = 0.0019 mg/kg-d

4.1.5 Adjustments to the $POD_{HED\text{-}oral}$ for PFOA

The following uncertainty factors (UFs) were applied to the TCEQ-calculated $POD_{HED\text{-}oral}$ of 0.0019 mg/kg-d:

- A UF_H of 10 was not applied because a publication (Zhang et al. 2013) is available that describes the variability in human clearance of PFOA. A total UF_H of approximately 26 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 factor of 8.4 for toxicokinetic intrahuman variability. This $UF_{H\text{-}TK}$ of 8.4 was based on differences in clearance measured among different human population groups from Zhang et al. (2013) (See Table 2 of this study). This is a more conservative and data-informed approach than utilizing the default $UF_{H\text{-}TK}$ of 3 (or 3.16 as the square root of 10).[l] Accordingly, TCEQ considers a factor of 8.4 to account for toxicokinetic intrahuman variability to represent a conservative yet not unreasonable value for use in conjunction with a conservatively estimated $POD_{HED\text{-}oral}$ based on the selected critical effect in laboratory animals (i.e., decreased pre-weaning growth rate in mice). The calculations are described below, as well as the reasons for choosing the conservative factor of 8.4 for toxicokinetic variability.
    - 0.79 mL/d-kg arithmetic mean *n*-PFOA (linear PFOA) clearance for men/older females as the less sensitive group (higher clearance) ÷ 0.094 mL/d-kg arithmetic mean 95% lower bound clearance for younger females as the more sensitive group (lower clearance) = 8.4
    - This approach is a more conservative than using the same type values based on clearance for the sum of PFOA isomers (i.e., 0.77 mL/d-kg ÷ 0.11 mL/d-kg = 7 for sum of linear and branched isomers) or the weighted arithmetic mean clearance for men

[l] This intrahuman variability toxicokinetic adjustment factor (8.4), replacing the default $UF_{H\text{-}TK}$ of 3, has scientific precedence in the peer-reviewed scientific literature as part of an international collaboration on the safe oral dose for PFOA (Burgoon et al. 2023).

and all females (i.e., younger and older) ÷ the arithmetic mean 95% lower bound clearance for *n*-PFOA for younger females as the more sensitive group (lower clearance) (i.e., 0.67 mL/d-kg ÷ 0.094 mL/d-kg = 7.1), and considerably more conservative than using the arithmetic mean clearance *n*-PFOA values for both the less sensitive and more sensitive groups, which would provide a value (2.7) similar to the default of 3 to account for toxicokinetic intrahuman variability (i.e., 0.79 mL/d-kg ÷ 0.29 mL/d-kg = 2.7).

- A UF_A of 3 (or 3.16 as the square root of 10) is applied for potential toxicodynamic differences between laboratory animals and humans ($UF_{A\text{-}TD}$). A $UF_{A\text{-}TK}$ is not applicable since an internal dose metric (serum concentration) was utilized.
- A UF_L is not applicable as a NOAEL-based serum concentration was utilized.
- A UF_{SUB} of 1 was used. The critical effect of decreased pre-weaning growth rate in pups is a developmental effect for which exposure occurred over a sensitive period of development. The UF_{SUB} is not applied when a developmental or other shorter-duration study with a critical window of exposure is the key study (TCEQ 2015). Consequently, a $UF_{SUB} > 1$ is not needed in consideration of this endpoint.
- A UF_D of 1 is applied for this well studied PFAS chemical consistent with Table 5-2 of TCEQ guidelines (TCEQ 2015). As stated in USEPA (2024a, Table 4-10) a UF_D of 1 is applied when the database for a contaminant contains a multitude of studies of adequate quality that encompass a comprehensive array of endpoints in various lifestages and populations and allow for a complete characterization of the contaminant's toxicity.

  In animals, comprehensive oral short-term, subchronic, and chronic studies in three species and several strains of laboratory animals have been conducted and published in the peer reviewed literature. Additionally, there are several neurotoxicity studies (including developmental neurotoxicity) and several reproductive (including one- and two-generation reproductive toxicity studies) and developmental toxicity studies including assessment of immune effects following developmental exposure.

$$\text{PFOA RfD} = POD_{HED\text{-}oral} / (UF_{H\text{-}TK} \times UF_{H\text{-}TD} \times UF_A \times UF_{SUB} \times UF_D)$$

$$= 0.0019 \text{ mg/kg-d} / (8.4 \times 3.16 \times 3.16 \times 1 \times 1)$$
$$= 0.0019 \text{ mg/kg-d} / 84$$
$$= 2.26\text{E-}05 \text{ mg/kg-d or } \mathbf{2.3E\text{-}05\ mg/kg\text{-}d} \text{ (at two significant figures)}$$

By comparison, the current Australian RfD for PFOA is 7-fold higher at 160 ng/kg-d or 1.6E-04 mg/kg-d. Additionally, as indicated previously, the Australian government most recently (October 2024) published a revisited draft assessment of PFOA. The current Australian RfD based on Lau et al. (2006) was considered high confidence, and the only high confidence draft candidate RfD for PFOA had a value of 115 ng/kg-d or 1.15E-04 mg/kg-d (non-neoplastic

hepatocellular necrosis in rats in NTP 2020, revised 2023), which is 5-fold higher than TCEQ's RfD.[m] Thus, the high confidence current and draft RfD values based on Australia's most recent PFOA assessment (October 2024) are 5- to 7-fold higher than TCEQ's PFOA RfD. In part, this is because TCEQ uses a total UF of 84 for the RfD derivation based on Lau et al. 2006 while Australia uses a total UF of 30.

4.1.6 PFOA Health-Based Chronic RfD

In deriving the RfD for PFOA, no numbers were rounded between equations until the RfD was calculated. The RfD was rounded to two significant figures (Table 7).

Table 7. Derivation of the Chronic RfD for PFOA and Associated Salts

Parameter	Summary
Study	Lau et al. (2006)
Study Population	Pregnant CD-1 mice, 9-45/group; 7-30 litters/group evaluated for neonatal body weights during pre-weaning
Study Quality	High
Exposure Method	Oral gavage to APFO
Exposure Duration	GD 1-18
Critical Effects	Decreased pre-weaning growth rate in pups
$POD_{Internal}$	15.8 mg/L average serum (NOAEL)
$POD_{HED\text{-}oral}$	0.0019 mg/kg-d (calculated using human clearance of 0.00012 L/kg-d)
Total UFs	84
Interspecies UF	3 (or 3.16 as the square root of 10)
Intraspecies UF	3 for toxicodynamics (or 3.16 as the square root of 10) 8.4 for toxicokinetics (based on data in Zhang et al. 2013)
LOAEL UF	N/A
Subchronic to chronic UF	1

[m] See Table 6-4 at: https://consultations.nhmrc.gov.au/environmental-health/australian-drinking-water-guidelines-2024-pfas/supporting_documents/SLR%202024%20Addendum%20to%20the%20Evidence%20Evaluation%20%20PFAS%20Evidence%20Review.pdf

Parameter	Summary
Incomplete Database UF Database Quality	1 high
PFOA RfD (HQ = 1)	**2.3E-05 mg/kg-d for APFO [a]**

a: When adjusted for differences in molecular weight, the RfD is 2.2E-05 mg/kg-d for perfluorooctanoic acid, 2.3E-05 mg/kg-d for sodium perfluorooctanoate, and 2.4E-05 mg/kg-d for potassium perfluorooctanoate.

4.1.7 Chronic Noncarcinogenic Observed Adverse Effect Level (OAEL) for PFOA

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, 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 $LOAEL_{HED\text{-}oral}$ was 0.0032 mg/kg-d (see Table 6), which was identified in Lau et al. (2006) for the critical effect of decreased pre-weaning growth in CD-1 mouse pups exposed to PFOA during gestation and lactation. Therefore, the OAEL for APFO is set at 0.0032 mg/kg-d. The MOE between the OAEL of 0.0032 mg/kg-d and the RfD is 139 times for APFO.

4.2.1 PFOS Key and Supporting Studies

4.2.1.1 PFOS Human Studies

Consideration of the weaknesses and limitations of the epidemiological study evidence for PFOS leads the TCEQ to conclude that although relevant for hazard identification, the associated epidemiologic results (e.g., immunotoxicity) are not sufficient for quantitative risk assessment and toxicity factor (e.g., RfD) derivation. This is consistent with conclusions of the Australian and New Zealand governments (FSANZ 2021), the Agency for Toxic Substances and Disease Registry (ATSDR; part of the U.S. Department of Health and Human Services), 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). Most recently, the October 2024 Public Consultation Draft for Per- and poly-fluoroalkyl substances (PFAS) by the Australian Government's National Health and Medical Research Council[n] (Australian NHMRC 2024) has concluded in regard to the use of epidemiological studies [*emphasis added*]:

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

> Other international assessments have considered benchmark doses calculated from low levels of PFOS in serum associated with decreased antibody formation following administration of certain vaccines in humans (Abraham et al. 2020, Budtz-Jorgensen and Grandjean 2018, Grandjean et al. 2012, Timmermann et al. 2022, Zhang et al. 2023). Based on a critical evaluation of these studies and *consistent with the conclusions made by FSANZ (2021), it was concluded that a causal relationship between increased PFAS serum levels (as a mixture including PFOS) and impaired vaccine response cannot be established with reasonable confidence from the available human epidemiological information* (SLR 2024a,b,c). 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 that endpoint to be used for derivation of a PFOS health-based guideline value*. Although the reduced antibody response following vaccination has been considered by some international assessments as the most 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 concurs with these conclusions. See Appendix 3 for additional details.

4.2.1.2 PFOS Animal Studies – Oral Route of Administration

To inform the derivation of a chronic oral RfD for PFOS and associated salts, TCEQ used information from multiple sources. TCEQ conducted a systematic review to identify and evaluate animal studies with oral exposure to PFOS (see Appendix 1 and TCEQ's PFAS Systematic Review (2025)). In addition, TCEQ reviewed assessments conducted by other state, federal, or international agencies that derived toxicity factors for PFOS. Part of the toxicity factor derivation process under the TCEQ (2015) guidelines involves consideration of adopting an existing assessment by another agency, with a critical criterion being whether the assessment is sufficiently consistent with how the TCEQ would conduct such an assessment. With this in mind, TCEQ may adopt all or part of another agency's assessment.

One recently available assessment for PFOS is the draft developed by the Australian NHMRC (2024), which is discussed below in Section 4.2.2 Selection of the Key Study(ies) and Critical Effects. TCEQ also used information from the USEPA Human Health Toxicity Assessment for PFOS and Related Salts (USEPA 2024b). Both agencies conducted a search of the available literature on PFOS. USEPA's systematic review is described in Chapter 2 of USEPA (2024b). For the Australian NHMRC (2024) assessment, Section 3 of *Evidence Evaluations for Australian Drinking Water Guidelines Chemical Fact Sheets – PFOS, PFHxS, PFOA, PFBS, and GenX*

Chemicals, Technical Report[o] summarizes the methods for evidence evaluation review conducted for five PFAS, including PFOS. Section 3 of that technical report provides sufficient detail for a third party to reproduce the search. Figure 3-1 of that section shows the overview of the literature search process followed, presented as a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram that describes the study selection process and numbers of records at each stage of screening (Moher et al. 2009). In USEPA's and the Australian NHMRC's assessments, the animal studies identified were consistent with those identified by TCEQ's systematic review

As discussed in subsequent sections, the key studies that TCEQ ultimately selected for PFOS were developmental toxicity studies in rats (Luebker et al. 2005a, b) and the co-critical effects are decreased pup weight and weight gain during lactation through PND 5 in the F_1 generation.

4.2.1.3 PFOS Reproductive and Developmental Studies – Oral Route of Administration

Visual data summaries for PFOS-induced developmental and reproductive effects observed in laboratory animal studies were obtained from USEPA (2024b) via HAWC (https://hawc.epa.gov/summary/assessment/100500248/visuals/) and are presented in Appendix 5. Results of these studies will be discussed briefly in Section 4.2.1.3.1, Section 4.2.1.3.2, and Section 4.2.2. These exposure response arrays helped to compare the LOAELs across various reproductive and developmental studies conducted in animals administered PFOS or associated salts.

4.2.1.3.1 Luebker et al. (2005a) – Oral Two Generation Reproductive and Developmental Study in Rats – Key Study

The objective of this study was to assess the effects of PFOS on reproduction and development following dosing before cohabitation, and through mating, gestation, and lactation across two generations in rats. Male and female Crl:CD® (SD)IGS BR VAF® rats (Charles River Laboratories, Raleigh, NC) were dosed via oral gavage with potassium PFOS formulated in deionized water with 2% Tween® 80 at doses of 0 (vehicle control), 0.1, 0.4, 1.6, or 3.2 mg/kg-d. F_0 males (approximately 10 wk old) were dosed for 42 days prior to mating through the mating period. F_0 females (approximately 10 wk old) were dosed for 42 days prior to mating, through the mating period, and through GD 9 of for rats assigned to caesarean sectioning (10/group), or through lactation day (LD) 20 for rats assigned to natural delivery (24-25/group). Upon weaning on LD 22 (i.e., PND 22), two male and two female F_1 pups, if available, were randomly selected from each litter to continue the study. Daily oral gavage dosing of these rats, at the same dose level as their F_0 parents, began on PND 22 (referred as LD 22 in the publication) and continued

[o] October 17, 2024; available at: https://www.nhmrc.gov.au/health-advice/environmental-health/water/PFAS-review/guideline-development#block-views-block-file-attachments-content-block-1

through PND 90. On approximately PND 90, males and females were mated with dosing continuing through cohabitation. Following cohabitation the F_1 males were terminated, and F_1 females were dosed through LD 20. On LD 21, all F_1 dams and F_2 pups were terminated.

PFOS exposure had no effect on mating and fertility.

At doses ≥ 0.4 mg/kg-d, F_0 males had decreased absolute food consumption on days 53-63, with decreased overall body weight gain. At doses ≥ 1.6 mg/kg-d, decreased absolute and relative food consumption in F_0 males was seen on days 1-42, as well as decreased body weights relative to controls.

In F_0 females, partial alopecia (hair loss) was seen with increased incidence at doses ≥ 0.4 mg/kg-d. At doses ≥ 1.6 mg/kg-d, decreased overall body weight gain during the pre-mating period, decreased body weight during gestation, decreased absolute and relative food consumption on LD 1-14, and increased number of dams with all pups dying on PND 1-4 (greater than historical control incidence) were seen in F_0 females. At the high-dose of 3.2 mg/kg-d, additional findings in F_0 females were decreased body weight and absolute and relative food consumption during pre-mating, decreased absolute food consumption during gestation, slight decreased in duration of gestation, decreased number of implantation sites per delivered litter, increased number of dams with stillborn pups, decreased liveborn pups per litter and increased stillborn pups per litter.

F_1 pups had delayed eye opening at doses ≥ 0.4 mg/kg-d. At doses ≥ 1.6 mg/kg-d, decreased pup weight and pup weight change per litter were seen on PND 1-21. Increased number of pups found dead or presumed cannibalized, decreased viability and lactation indices, and developmental delays (delayed pinna unfolding, delayed surface and air righting) were observed at doses ≥ 1.6 mg/kg-d. In the 3.2 mg/kg-d group, all pups were dead by PND 2. Due to poor condition, pups in the 1.6 mg/kg-d group did not continue in the study past weaning.

In the F_2 pups, decreased weights were observed on PNDs 7 and 14, and decreased pup weight gain on PND 4-7 and PND 7-14 were observed in the 0.4 mg/kg-d group.

The NOAEL for mating and fertility was the high-dose of 3.2 mg/kg-d. The LOAEL and NOAEL for paternal toxicity were 0.4 and 0.1 mg/kg-d, respectively, due to decreased absolute food consumption during mating and decreased overall body weight gain in comparison to controls. The LOAEL and NOAEL for maternal toxicity were 1.6 and 0.4 mg/kg-d, respectively, due to decreased body weight gain and food consumption, and increased number of dams with all pups dying on PND 1-4. In F_1 pups, the LOAEL and NOAEL for developmental toxicity were 0.4 and 0.1 mg/kg-d, respectively, due to delayed eye opening. Lastly, the LOAEL and NOAEL in the F_2 pups were 0.4 and 0.1 mg/kg-d, respectively, due to decreased body weight and body weight gain.

4.2.1.3.2 Luebker et al. (2005b) – Oral Developmental Study to Assess Neonatal Mortality – Key Study

This study was a follow-up study to the two-generation reproductive and developmental study in rats. The objective was to better define the dose-response curve for neonatal mortality in pups born to PFOS-dosed dams. Therefore, this study included additional doses of 0.8, 1.0, 1.2, and 2.0 mg/kg-d, but did not include the dose of 3.2 mg/kg-d due to severe toxicity (refer to Section 4.2.1.3.1). Male and female Crl:CD®(SD)IGS VAF/Plus® rats (Charles River Laboratories) were used for this study. F_0 females (approximately 11 wk old) were dosed via oral gavage with potassium PFOS formulated in deionized water with 2% Tween® 80 at doses of 0 (vehicle control), 0.4, 0.8, 1.0, 1.2, 1.6, or 2.0 mg/kg-d for 42 days prior to mating (with non-dosed males) through GD 20 for caesarean sectioning, or LD 4 for natural delivery. Twenty dams/group were assigned for natural delivery and pups and dams were terminated on LD 5.

PFOS exposure had no effect on mating and fertility. In dams dosed at ≥ 0.8 mg/kg-d, decreased relative food consumption and body weight gain during lactation, and increased relative liver weight (to body weight) on GD 21 were seen. In the 1.6 and 2.0 mg/kg-d groups, dams had decreased absolute food consumption during gestation and lactation and decreased body weight during gestation; other findings included increased number of dams with all pups dying during PND 1-5 and a decreased pup viability index on PND 5. In the 2 mg/kg-d group, dams also had decreased absolute and relative food consumption and decreased body weight gain during pre-mating, and decreased body weight during lactation.

Decreased pup weight per litter at birth and on PND 5 and decreased pup weight gain per litter through PND 5 occurred at doses ≥ 0.4 mg/kg-d. At ≥ 1.6 mg/kg-d, there was decreased pup survival on PND 5.

The NOAEL for mating and fertility was the high-dose of 2.0 mg/kg-d. The LOAEL and NOAEL for maternal toxicity were 0.8 and 0.4 mg/kg-d, respectively, due to decreased relative food consumption and body weight gain during lactation and increased relative liver weight in the dams. The LOAEL for neonatal development was 0.4 mg/kg-d due to decreased pup weight at birth and on PND 5. Note that this is the same LOAEL for neonatal development, which was also due to the effect of decreased pup weight, reported in the two-generation reproductive and developmental study in rats (Luebker et al. 2005a).

4.2.2 Selection of the Key Study(ies) and Critical Effects for PFOS

Because of the large number of PFOS animal studies, TCEQ used summary information from the Australian NHMRC (2024)[p] to focus on studies that were most likely to be candidate key

[p] Available at: https://consultations.nhmrc.gov.au/environmental-health/australian-drinking-water-guidelines-2024-pfas/supporting_documents/SLR%202024%20Evidence%20Evaluation%20Report%20%20PFAS%20Evidence%20Review.pdf

studies. NHMRC (2024) evaluated ten health-based guidance values for PFOS from international jurisdictions for potential adoption or adaptation. However, only two guidance values used data in the RfD derivation that had previously not been considered and evaluated by the Australian and New Zealand governments (FSANZ 2017b). These were the EFSA (2020a) and USEPA (2022c,e; 2021b) guidance values for PFOS, which used two studies (i.e., Abraham et al. 2020, Budtz-Jørgensen and Grandjean 2018) to underpin the derivation that had not been previously considered/evaluated by FSANZ (2017b). Based on a critical evaluation of these two studies, consistent with the conclusions made by FSANZ (2021), NHMRC (2024) concluded that a causal relationship between increased PFAS serum levels and impaired vaccine response cannot be established with reasonable confidence from the available human epidemiological information. The evidence for an association between increasing PFAS serum levels and impaired vaccine response is insufficient for the endpoint to be used for derivation of PFOS toxicity factors (e.g., an RfD). NHMRC (2024) therefore concluded the current Australian guidance value for PFOS (20 ng/kg-d) is still appropriate. The derivation of this health-based guidance value (i.e., RfD), for which confidence is high, was based on the two-generation reproductive and developmental study in rats (Luebker et al. 2005a).

Accordingly, the current calculated RfD value from Australia is 17 ng/kg-d, or 1.7E-05 mg/kg-d, which was then rounded to 20 ng/kg-d (2.0E-05 mg/kg-d), based on significantly decreased pup weight (a developmental effect) in Luebker et al. (2005a).

In addition, an NHMRC (2025) *Addendum to PFAS Evidence Evaluation for Australian Drinking Water Guidelines Chemical Fact Sheets to the 2024 PFAS Review*[q] considered the USEPA April 2024 health effects documentation for PFOS (USEPA 2024b).[r] In the Addendum, draft RfDs were derived based on decreased extramedullary hematopoiesis and bone marrow hypocellularity in the 28-day rat gavage NTP (2022) study, and decreased plaque forming cell response (sheep red blood cell-specific IgM production by B lymphocytes isolated from the spleen) in a developmental immunotoxicity study in mice (Zhong et al. 2016).

In addition to the candidate studies identified in NHMRC (2024) and NHMRC (2025), TCEQ also considered the results of the 6-month toxicity study in cynomolgus monkeys (Seacat et al. 2002) because monkeys are more physiologically similar to humans than rodents. TCEQ also considered Luebker et al. (2005b), the follow-up study to the two-generation reproductive and developmental study in rats (Luebker 2005a), because it was conducted to better define the dose response of neonatal mortality in rats (Luebker et al. 2005b) was considered by the TCEQ. Note that TCEQ used the internal dose values and human clearance values that are in USEPA

[q] Available at: https://consultations.nhmrc.gov.au/environmental-health/australian-drinking-water-guidelines-2024-pfas/supporting_documents/SLR%202024%20Addendum%20to%20the%20Evidence%20Evaluation%20%20PFAS%20Evidence%20Review.pdf

[r] This resulted in the critical review of an additional 19 studies for PFOA and/or PFOS.

(2024b) in the derivation of an RfD. The candidate key studies along with LOAELs and $LOAELs_{HED\text{-}oral}$ are shown in Table 8. $LOAELs_{HED\text{-}oral}$ values are particularly relevant since TCEQ identifies the critical effects based on comparison of $LOAEL_{HED}$ values (based on human equivalent dose-response effect levels), not based on comparison of values that include uncertainty factors. TCEQ's method is consistent with the definition of critical effect (TCEQ 2015)[s], because greater uncertainty can overcome greater observed sensitivity of an endpoint, potentially resulting in the selection of the most uncertain endpoint as the critical effect.

[s] The critical effect is basically the first adverse effect as the dose rate increases, which is commonly documented in a study as the study- and endpoint-specific LOAEL and/or an overall study LOAEL. The first adverse effect that may be expected to occur in humans as the dose rate increases can be determined on the basis of comparing $LOAEL_{HED}$ values (TCEQ 2015).

Table 8. Candidate key studies, adverse effects, LOAELs, and $LOAELs_{HED\text{-}oral}$ for PFOS

Study	Species	Dosing Duration	Adverse effect	LOAEL (mg/kg-d)	Internal dose (mg/L)	$LOAEL_{HED\text{-}oral}$ [a] (mg/kg-d)
Two-generation reproductive and developmental study (Luebker et al. 2005a) [b]	Crl:CD® (SD)IGS BR VAF® rats	See footnote c for details	F1 pups: slight delay eye opening F2 pups: decreased weights PNDs 7 and 14; decreased pup weight change PND 4-7 and PND 7-14	0.4	15.9 [d]	2.0E-03
Developmental study to assess neonatal mortality (Luebker et al. 2005b) [e]	Crl:CD® (SD)IGS BR VAF® rats	F: 42 days prior to mating through GD 20 or LD 4	F1 pups: decreased pup weight/litter at birth and on PND 5; decreased pup weight gain/litter through PND 5	0.4	15.4 [f]	2.0E-03
Developmental immunotoxicity study (Zhong et al. 2016)	C57BL/6 mice	GD 1-17	Decreased ex vivo sheep red blood cell (SRBC)-specific IgM production (plaque forming cell response) in spleen cells of males at 4 wk old, decreased ex vivo spleen natural killer (NK) cell activity in males at 8 wk old	1	16.8 [g]	2.1E-03
Short-term toxicity study (NTP 2022)	Sprague Dawley (HSD: Sprague Dawley SD) Rats	28 days	Spleen: minimal decreased extramedullary hematopoiesis in females	1.25	40.0 [h]	5.1E-03
Short-term toxicity study (NTP 2022)	Sprague Dawley (HSD: Sprague Dawley SD) Rats	28 days	Spleen: minimal decreased extramedullary hematopoiesis in males Bone marrow: minimal hypocellularity in males	1.25	40.8 [i]	5.2E-03
Two-generation reproductive and developmental study (Luebker et al. 2005a) [b]	Crl:CD® (SD)IGS BR VAF® rats	See footnote c for details	Paternal toxicity: decreased overall body weight gain and decreased food consumption	0.4	45.4 [j]	5.8E-03

Study	Species	Dosing Duration	Adverse effect	LOAEL (mg/kg-d)	Internal dose (mg/L)	$LOAEL_{HED\text{-}oral}$ [a] (mg/kg-d)
Chronic toxicity study (Seacat et al. 2002)	Cynomolgus monkeys	Up to 6 months	Decreased total T_3 in females on Days 91, 182 and 184, decreased total T_4 in females on Days 37, 62, 91 and 182	0.15	66.8 (F) [k]	8.5E-03
Developmental study to assess neonatal mortality (Luebker et al. 2005b) [e]	Crl:CD® (SD)IGS BR VAF® rats	F: 42 days prior to mating through GD 20 or LD 4	Maternal toxicity: decreased relative food consumption and body weight gain during lactation; increased relative liver weight on GD 21	0.8	N/A [l]	N/A
Two-generation reproductive and developmental study (Luebker et al. 2005a) [b]	Crl:CD® (SD)IGS BR VAF® rats	See footnote c for details	Maternal toxicity: increased dams with pups dying PND 1-4; decreased body weight gain during pre-mating; decreased body weight during gestation; decreased food consumption during lactation	1.6	82 [m]	1.0E-02

Abbreviations: F, female; GD, gestation day; LD, lactation day; LOAEL, lowest-observed-adverse-effect-level; $LOAEL_{HED\text{-}oral}$, lowest-observed-adverse-effect-level human equivalent oral dose M, male; N/A, not available; T_3, triiodothyronine; T_4, thyroxine
a: calculated using a human clearance of 0.000128 L/kg-d (Table 4-6 in USEPA 2024b)
b: Basis for FSANZ toxicity factor (referred to as Luebker et al. 2005b in relevant documents; USEPA refers to this study as Luebker et al. 2005a)
c: In this multigeneration study, F0 males were dosed 42 days prior to mating and through mating (maximum of 14 days) and terminated after co-habitation. F0 females were dosed 42 days prior to mating through Gestation Day (GD) 9 or Lactation Day (LD) 20. Upon weaning, F1 male and female pups (2/sex/litter) were dosed at the same doses as F0 parents. F1 generations dosed were dosed from LD 22 to postnatal day (PND) 90 and mated. Dosing continued through mating (maximum of 14 days). Male F1 rats terminated after co-habitation. Pregnant F1 rats dosed through LD 20. F1 dams and F2 pups terminated on LD 21
d: Value from Table E-57 in USEPA 2024b
e: Basis for candidate RfD in USEPA 2024b. USEPA refers to this study as Luebker et al. 2005b
f: Value from Table E-59 in USEPA 2024b for pup weight at birth (LD 1); modeled serum concentration on LD 5 is 15.9 mg/L
g: Value from Table E-65 in USEPA 2024b
h: Value from Table E-63 in USEPA 2024b
i: Value from Table E-61 in USEPA 2024b
j: Value from p. 137, right column, second paragraph – serum concentrations in F0 males (Luebker et al. 2005a)
k: Value from Table 1 in Seacat et al. 2002
l: Serum concentrations not measured in the 0.8 mg/kg-d group in this study. Refer to Table 9 in the publication. Mean serum concentrations in dams from GD 1-21 at 0.4 mg/kg-d and 1.6 mg/kg-d were 37.3 and 151.5 mg/L, respectively. Based on this, the mean serum concentration at 0.8 mg/kg-d in dams would not achieve the lowest $LOAEL_{HED\text{-}oral}$.
m: p. 137, right column, second paragraph – serum concentrations in F1 females on LD 21

The NHMRC considered the two-generation reproductive and developmental study in rats (Luebker 2005a) to be of high confidence. USEPA (USEPA 2024b) utilized the neonatal mortality

study (Luebker 2005b) for a candidate RfD and deemed this study to be of medium confidence. Both NHMRC and USEPA considered the histopathologic findings in the spleen and bone marrow in the 28-day oral gavage toxicity study in rats (NTP 2022) for candidate RfDs and both agencies considered this study to be of high confidence. The developmental immunotoxicity study in mice (Zhong et al. 2016) also was used by both agencies in development of candidate RfDs and both agencies deemed this study to be of medium confidence. The 6-month toxicity study in cynomolgus monkeys (Seacat et al. 2002) was considered a high-confidence study by TCEQ.

The co-critical effects of slight delay in eye opening in F1 pups and decreased body weight and body weight gain in F2 pups in the multigeneration study in rats (Luebker et al. 2005a), and of decreased pup weight per litter and pup weight gain per litter through PND 5 in the follow-up neonatal mortality study in rats (Luebker et al. 2005b), had the lowest $LOAEL_{HED\text{-}oral}$ of 2.0E-03 mg/kg-d. A slightly higher $LOAEL_{HED\text{-}oral}$ of 2.1E-03 mg/kg-d was associated with decreased plaque forming cell response (sheep red blood cell-specific IgM production by B lymphocytes isolated from the spleen) in a developmental immunotoxicity study in 4-week old male mice and decreased natural killer cell activity in 8-week old male mice exposed to PFOS in utero (Zhong et al. 2016). The $LOAEL_{HED\text{-}oral}$ associated with the co-critical developmental effects in rats also was 2.5- to 2.6-fold lower than the $LOAELs_{HED\text{-}oral}$ for effects in the spleen and bone marrow in the 28-day study in rats. The LOAEL in the 6-month toxicity study in male and female cynomolgus monkeys (Seacat et al. 2002) was 0.15 mg/kg-d. The adverse effect was decreased total triiodothyronine (T_3) and total thyroxine (T_4) in females. Due to the potential for interference of PFAS in measurement of thyroid hormones using radioimmunoassay, the samples for all intervals were analyzed by a laboratory using radioimmunoassay and the samples collected at termination were verified by a second laboratory using equilibrium dialysis followed by radioimmunoassay for free T_4 and standardized chemiluminometric immunoassays for other thyroid hormones. The $LOAEL_{HED\text{-}oral}$ of 8.5E-03 mg/kg-d in cynomolgus monkeys was 4.2-fold higher than the $LOAEL_{HED\text{-}oral}$ for developmental effects in rats. Lastly, the $LOAELs_{HED\text{-}oral}$ for paternal and maternal toxicity in the multigeneration and neonatal mortality studies in rats (Luebker et al. 2005a, Luebker et al. 2005b) were 2.9- to 5-fold higher than the $LOAEL_{HED\text{-}oral}$ for the co-critical effects. Based on the comparison of $LOAELs_{HED\text{-}oral}$, because the $LOAEL_{HED\ oral}$ associated with developmental effects in rats is the lowest $LOAEL_{HED\text{-}oral}$, the developmental effects in rats reported in Luebker et al. (2005a, 2005b) will be the co-critical effects.

USEPA (USEPA 2024b) modeled the serum concentrations in pups to include exposure during gestation only for effects on PND 1, and for exposure during gestation and lactation for effects on PND 5. USEPA performed benchmark dose (BMD) modeling using a BMR of 5% (BMD_5) for neonatal weight for both Luebker et al. 2005a and 2005b. The results are shown in Tables E-58, E-60, and E-70 (USEPA 2024b). TCEQ also performed BMD modeling using BMDS online version 25.1 for the internal doses and neonatal body weights reported in Tables E-57, E-59 and E-69

(USEPA 2024b); TCEQ also derived benchmark doses at a 5% response (BMD_5) and benchmark dose lower confidence limits at a 5% response ($BMDL_5$). The Benchmark Dose Software (BMDS) modeling performed by TCEQ confirmed the BMDS modeling results reported in USEPA (2024b). For the pup weight on PND 5 (Luebker et al. 2005b), all models were unusable when all the data were modeled. When the highest dose was dropped, all but one of the models were viable. Considering $p > 0.1$, the absolute value of scaled residuals < 2, BMD lower confidence limit (BMDL) values within 3-fold, and lowest Akaike index criterion (AIC), the model selected by TCEQ is the exponential 3 model (BMD_5 of 10.8 mg/L, $BMDL_5$ of 7.3 mg/L) for decreased pup weight on PND 5. For pup weight on PND 1 in Luebker et al. 2005b, the model with the best fit was the exponential 3 model with a BMD_5 of 22.6 mg/L and a $BMDL_5$ of 14.7 mg/L. Using BMDS online version 25.1, for pup weight on PND 1 in Luebker et al. 2005a, the exponential 5 model had the best fit with a BMD_5 of 25.8 mg/L and a $BMDL_5$ of 12.1 mg/L. Note that BMDS modeling performed by USEPA (2024b, refer to table E-70) provided additional models and USEPA selected the exponential 4 model, which had the lowest AIC, with a a BMD_5 of 17.7 mg/L and a $BMDL_5$ of 11.3 mg/L; the results for BMD_5 and $BMDL_5$ for the exponential 5 model were the same in USEPA (2024b) as those obtained when using BMDS online version 25.1. Based on the BMD modeling performed by USEPA and TCEQ, the lowest $BMDL_5$ of 7.3 mg/L for pup weight on PND 5 from Luebker et al. (2005b) was used by TCEQ for derivation of the RfD. This serum concentration is based on the most sensitive effect (i.e., significantly decreased pup weight) identified under TCEQ (2015) guidelines (i.e., comparing $LOAEL_{HED}$ values) of the candidate endpoints considered suitable for candidate RfD derivation. The corresponding $POD_{HED\text{-}oral}$ was calculated to be 0.00093 mg/kg-d (more details provided in Section 4.2.4.3).

Moreover, based on laboratory animal data for PFOS-induced developmental and reproductive endpoints summarized by USEPA (2024b; https://hawc.epa.gov/summary/assessment/100500248/visuals/, see Appendix 5), an RfD derived based on a POD of 0.00093 mg/kg-d from Luebker et al. (2005b) would also be expected to be protective of other developmental effects and reproductive endpoints, given the MOE. Regarding other developmental effects, Lee et al. (2015) reported a significantly higher incidence of resorptions, post-implantation loss, and dead fetuses at GD 17 after dosing pregnant CD-1 mice by gavage with 0.5, 2, or 8 mg/kg-day on GD 11-16. By contrast, in Fuentes et al. (2006), CD-1 mice were dosed with 0, 1.5, 3, or 6 mg/kg-day PFOS on GD 6-18 with no PFOS-related effects on the number of litters with dead fetuses, total number of dead fetuses, dead fetuses per litter, and live fetuses per litter, and there were no effects of PFOS on the number of implantation sites, the percentage of post-implantation loss, the number of early or late resorptions, mean fetal weight, and fetal sex ratio. Consequently, the reported mouse LOAEL (0.5 mg/kg-d) from Lee et al. (2015), in addition to being higher than that from Luebker et al. (2005a and 2005b), had findings that conflicted with the results from similar studies, making it not appear to be sufficiently reliable for dose-response assessment and derivation of an RfD. Reproductive effect levels (see Appendix 5.4 PFOS Reproductive Endpoints) from

various studies were either higher than the LOAEL (0.4 mg/kg-d) from Leubker et al. (2005a, 2005b) and/or represent endpoints for which a candidate RfD cannot be derived with sufficient confidence (e.g., effect does not necessarily rise to the level of adversity, non-monotonic and/or inconsistent with other study results such as testosterone levels in Alam et al. 2012). The RfD based on co-critical effects from Luebker et al. (2005a, 2005b), utilizing the $BMDL_5$ from Luebker et al. (2005b), would be expected to be protective against demonstrated developmental/reproductive effects. To this point, USEPA (2024b) did not derive candidate RfD values based on these other developmental/reproductive effects, but did calculate a candidate RfD based on decreased pup weight on PND 5 from Luebker et al. (2005b).

The TCEQ derived a $POD_{HED\text{-}oral}$ of 0.00093 mg/kg-d corresponding to the $BMDL_5$ of 7.3 mg/L (internal dose) for a developmental effect (i.e., decreased pup weight on PND 5) based on Luebker et al. (2005b) for derivation of the TCEQ's RfD for PFOS. This is consistent with TCEQ's consideration of NHMRC 2024/FSANZ 2017 under the TCEQ toxicity factor guidelines (TCEQ 2015), other animal data for various effects (e.g., developmental, reproductive), as well as the agency's determination that the available epidemiological data are unsuitable for quantitative dose-response assessment and toxicity factor derivation (e.g., issues of confounding co-exposures and biological significance/adversity; see Appendix 3), which is consistent with relatively recent evaluations by other agencies (e.g., FSANZ 2021, ATSDR 2021, Australian NHMRC 2024).

4.2.3 MOA Analysis and Dose Metric for PFOS

See USEPA (2024b) for thorough discussions of the MOA data relevant to PFOS-induced developmental effects. Briefly, evidence from mechanistic studies that relates to observed developmental effects of PFOS is limited. Developmental studies in animals show dose-related maternal and offspring effects; however, a few studies in rodents did not show effects. Developmental effects include increased mortality (fetal and neonatal), effects on fetal, neonatal, and maternal body weight, and developmental delay (e.g., delayed eye opening). In the key studies (Luebker et al. 2005a and 2005b), the body weight effects and delayed eye opening in rats occur at doses that do not produce maternal body weight changes or other apparent maternal effects and therefore are not considered to be due to maternal toxicity. The effects on body weight and growth in pre-weaned pups are threshold effects, and the key studies (Luebker et al. 2005a and 2005b) identified a NOAEL and LOAEL for decreased growth in pups prior to weaning, and a $BMDL_5$ was derived for this effect.

The dose metric is the internal dose of PFOS from USEPA (2024b, refer to Section E.2.3.1 and exponential model result in Table E-58; TCEQ selected the exponential 3 model with a $BMDL_5$ of 7.3 mg/L based on $p > 0.1$, the absolute value of scaled residuals < 2, BMDL values within 3-fold, and lowest AIC). Because the critical effect of decreased preweaning growth rate from Luebker et al. (2005b) is a developmental effect and the pups were exposed during gestation and

lactation, the internal dose represents the average concentration normalized per day during these relevant exposure windows in the study (i.e., gestation and lactation). The PBPK model used to calculate the internal dose (Wambaugh 2013) is described further in Section 4.1.3.1.3 in USEPA (2024b).

4.2.4 Adjustments to the POD for PFOS

4.2.4.1 Dosimetry Adjustments from Animal-to-Human Exposure and Serum-to-Oral Dose for PFOS

As stated in Section 4.2.2, the TCEQ derives a $POD_{HED\text{-}oral}$ of 0.00093 mg/kg-d corresponding to the $BMDL_5$ (7.3 mg/L) for a developmental effect (i.e., decreased pup weight on PND 5) based on Luebker et al. (2005b) for derivation of the TCEQ's RfD for PFOS. Because this POD is based on the serum concentration associated with the $BMDL_5$ (7.3 mg/L) as the internal dose metric, derivation of an oral RfD expressed as mg/kg-d required extrapolation from a serum concentration ($POD_{HED\text{-}serum}$) to human oral dose ($POD_{HED\text{-}oral}$) using a human clearance value of 0.000128 L/kg-d (Table 4-6 in USEPA 2024b).

Briefly, the $POD_{HED\text{-}oral}$ value for Luebker et al. (2005b) was based on the average serum concentration derived from the predicted area under the curve (AUC) over the duration of dosing using the USEPA PK model and parameters (Wambaugh et al. 2013, refer to Section 4.1.3.1.3 of USEPA 2024b). The data (Table E-57 in USEPA 2024b) were modeled using USEPA's BMDS and the model selected resulted in a $BMDL_5$ serum concentration of 7.3 mg/L. The $BMDL_5$ serum PFOS concentration was converted to a $POD_{HED\text{-}oral}$ value using the following equation:

$POD_{HED\text{-}oral}$ value = serum concentration (mg/L) × CL (in human)

where CL (in human) = 0.000128 L/kg-d for PFOA (section 4.1.3.2 in USEPA 2024b)

Thus, the $POD_{HED\text{-}oral}$ = 7.3 mg/L ($POD_{HED\text{-}serum}$) × 0.000128 L/kg-d = 0.00093 mg/kg-d

4.2.5 Adjustments to the $POD_{HED\text{-}oral}$ for PFOS

The following uncertainty factors (UFs) were applied to the $POD_{HED\text{-}oral}$ of 9.3E-04 mg/kg-d:

- 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 that a toxicokinetic intrahuman variability factor of 2.1 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 $POD_{HED\text{-}oral}$ based on a sensitive critical (i.e., developmental) effect in laboratory animals. The calculations to generate the alternative toxicokinetic factor of 2.1 are described below, as well as the reasons for choosing the default factor of 3 for toxicokinetic variability.

  - 0.045 mL/d-kg arithmetic mean *n*-PFOS (linear PFOS) clearance for younger females as the less sensitive group (higher clearance) ÷ 0.021 mL/d-kg arithmetic mean 95% lower bound clearance for men/older females as the more sensitive group (lower clearance) = 2.1. Values derived using other possible clearance rates generated even smaller levels of variance between human populations. For example, using clearance for the sum of PFOS isomers (i.e., 0.05 mL/kg-d ÷ 0.026 mL/kg-d = 1.9) or the arithmetic mean clearance for younger females ÷ the weighted arithmetic mean 95% lower bound clearance for *n*-PFOS for men and all females (i.e., younger and older) as the more sensitive group (lower clearance) (i.e., 0.045 mL/d-kg ÷ 0.024 ml/d-kg = 1.9). This also is more conservative than using the arithmetic mean *n*-PFOS clearance values for both the less sensitive and more sensitive groups (i.e., 0.045 mL/d-kg ÷ 0.031 mL/d-kg = 1.5).

- A UF_A of 3 is applied for potential toxicodynamic differences between laboratory animals and humans ($UF_{A\text{-}TD}$). A $UF_{A\text{-}TK}$ is not applicable since an internal dose metric (serum concentration) was utilized.

- A UF_L is not applicable as a $BMDL_5$-based serum concentration was utilized.

- A UF_{SUB} of 1 was used. Luebker et al. (2005b) was a developmental study in which female F0 rats were dosed 42 days prior to mating, throughout mating, and GD 20 for rats assigned to caesarean sectioning, or LD 4 for rats assigned to natural delivery. The other key study with the same critical effect and co-critical effects (Luebker et al. 2005a) was a two-generation study during which female F_0 rats were dosed 42 days prior mating, throughout mating, and GD 9 for rats assigned to caesarean-sectioning, or LD 20 for rats assigned to natural delivery. Upon weaning, daily dosing of F_1 pups began on LD 22 for subsequent mating. The critical effect of significant decreased pup weight is a developmental effect for which exposure occurred over a sensitive period of development. The UF_{SUB} is not applied when a developmental or other shorter-duration study with a critical window of exposure is the key study (TCEQ 2015). Consequently, a UF_{SUB} >1 is not needed in consideration of these endpoints.

- A UF_D of 1 is applied for this well studied PFAS chemical consistent with Table 5-2 of TCEQ guidelines (TCEQ 2015). As stated in USEPA (2024b, Table 4-10) a UF_D of 1 is applied when the database for a contaminant contains a multitude of studies of adequate quality that

encompass a comprehensive array of endpoints in various lifestages and populations and allow for a complete characterization of the contaminant's toxicity.

In animals, comprehensive oral short-term, subchronic, and chronic studies in three species and several strains of laboratory animals have been conducted and published in the peer-reviewed literature. Additionally, there are several neurotoxicity studies (including developmental neurotoxicity) and several reproductive (including one- and two-generation reproductive toxicity studies) and developmental toxicity studies including assessment of immune effects following developmental exposure.

PFOS RfD = $POD_{HED\text{-}oral}$ / ($UF_H \times UF_A \times UF_{SUB} \times UF_D$)

= 9.3E-04 mg/kg-d / (10 × 3 × 1 × 1)
= 9.3E-04 mg/kg-d / 30
= **3.1E-05 mg/kg-d** (at two significant figures)

By comparison, Australia's current calculated RfD value (1.7E-05 mg/kg-d) is approximately 1.8-fold lower than TCEQ's PFOS RfD value, due to the differences in internal dose and human clearance values used. Also note that Australia did round up the RfD to one significant figure (2E-05 mg/kg-d). However, the same composite uncertainty factor was used by Australia and both RfDs are based on a sensitive developmental effect (i.e., significant decreased pup weight) in one of the Luebker et al. studies (2005b).

4.2.6 PFOS Health-Based Chronic RfD

In deriving the RfD for PFOS, no numbers were rounded between equations until the RfD was calculated. The RfD was rounded to two significant figures (Table 9).

Table 9. Derivation of the Chronic RfD for PFOS and Associated Salts

Parameter	Summary
Study	Luebker et al. (2005b), Luebker et al. (2005a) for same critical effect and co-critical effects at the LOAEL
Study Population	Crl:CD(SD)IGS BR VAF rats
Study Quality	Medium
Exposure Method	Oral gavage to potassium PFOS
Critical Effects	Decreased pup weight and weight gain during lactation in F_1 generation, PND 5
Exposure Duration	Female F_0 rats were dosed 42 days prior mating, throughout mating, and day 9 of presumed gestation for rats assigned to caesarean-sectioning, or LD 20 for rats assigned to natural delivery. Upon weaning, daily dosing of F_1 pups began on LD 22 through subsequent mating (beginning on PND 90) and through LD 20 for the F_1 dams.
$POD_{Internal}$	7.3 mg/L average serum ($BMDL_5$)
$POD_{HED\text{-}oral}$	9.3E-04 mg/kg-d
Total UFs	30
Interspecies UF	3
Intraspecies UF	10
LOAEL UF	N/A
Subchronic to chronic UF	1
Incomplete Database UF *Database Quality*	1 high
PFOS RfD (HQ = 1)	**3.1E-05 mg/kg-d for potassium PFOS** [a]

a: When adjusted for differences in molecular weight, the RfD is 2.9E-05 mg/kg-d for perfluorooctane sulfonic acid, 3.0E-05 mg/kg-d for ammonium perfluorooctane sulfonate and sodium perfluorooctane sulfonate.

4.2.7 Chronic Noncarcinogenic OAEL for PFOS

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, 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 $LOAEL_{HED\text{-}oral}$ for PFOS exposure was 0.002 mg/kg-d (see Table 8), which was identified in Luebker et al. (2005a and 2005b). The co-critical effects were decreased neonatal pup weights through PND 14 and delayed eye opening in SD rats. Therefore, the OAEL for potassium PFOS is set at 0.002 mg/kg-d. The MOE between the $LOAEL_{HED\text{-}oral}$ of 0.002 mg/kg-d and the RfD is 64 times for potassium PFOS.

4.3 Carcinogenic Potential

4.3.1 Carcinogenic Weight of Evidence for PFOA

4.3.2 Key and Supporting Studies

4.3.2.1 Human/Epidemiological Studies

As discussed elsewhere herein (e.g., Section 4.1.1.1), consideration of the weaknesses and limitations of the epidemiological study evidence leads the TCEQ to conclude that although relevant for hazard identification, the available epidemiology studies are not sufficient for quantitative risk assessment and toxicity factor (e.g., SFo) derivation. This is consistent with conclusions of the Australian and New Zealand governments (FSANZ 2021), the Agency for Toxic Substances and Disease Registry (ATSDR; part of the U.S. Department of Health and Human Services), a number of earlier opinions from national agencies and organizations such as Danish EPA (2016), Expert Health Panel for PFAS (2018), and Kirk et al. (2018), and most recently, the Australian Government's National Health and Medical Research Council (NHMRC 2024). TCEQ concurs with these national and international agencies that due to critical weaknesses and limitations, the epidemiological data are insufficient for dose-response assessment and toxicity factor derivation. See Appendix 6 for additional details.

4.3.2.2 Animal Studies – Oral Route of Administration

Based on TCEQ's systematic review, as well as evaluation of the relevant literature that has been conducted by USEPA (2024a), three carcinogenicity studies were identified in which PFOA was admixed into the diet fed to Sprague Dawley rats (NTP 2020, revised 2023; Butenhoff et al. 2012a; Biegel et al. 2001). Statistically significant increases in tumors were seen in male rats

only. Male rats exposed to PFOA had increased incidences of hepatocellular tumors, pancreatic acinar cell tumors, and Leydig cell adenomas in the testis.

Part of the toxicity factor derivation process under TCEQ (2015) guidelines is consideration of adopting an existing assessment by another agency, with a critical criterion being if the assessment is sufficiently consistent with how TCEQ would conduct such an assessment. With this in mind, the TCEQ may adopt all or part of another agency's assessment. While TCEQ concurs with other national and international agencies that the epidemiological data are insufficient for dose-response assessment and toxicity factor (e.g., SFo) derivation, carcinogenic analyses based on animal data are available in recent USEPA assessments for PFOA (USEPA 2024a). Consistent with TCEQ guidelines (TCEQ 2015), these carcinogenic dose-response analyses based on laboratory animal data and the resulting SFo candidate values are considered for adoption herein. See Section 4.3.4 and other relevant sections below.

4.3.2.2.1 NTP (2020, revised 2023) Oral Carcinogenicity Study of PFOA in Rats

Due to concern that exposure to PFOA during early life development could lead to a higher probability of carcinogenic effects than adult-only exposure, these studies were designed with inclusion of groups of rats that had been exposed to PFOA prenatally (in utero) and postnatally (via milk during the preweaning period), and subsequently postweaning for 2 years with PFOA admixed into the diet. The prenatal (gestational)/postnatal (lactational) exposure was referred to as perinatal exposure in the report. Separate groups of rats were only exposed postnatally beginning on PND 22. In these Good Laboratory Practice (GLP)-compliant studies, time-mated 12-14 week old female Sprague Dawley rats (Hsd:Sprague Dawley ® SD® rats, Harlan Inc. [now Engivo] from Madison, WI for study in females or Indianapolis, IN for study in males) were fed PFOA in the diet at concentrations of 0, 150, or 300 ppm from GD 6 to PND 21.

Doses consumed by the dams in the 150 and 300 ppm groups during gestation were 10.9 and 21.7 mg/kg-d, respectively, and during lactation were 23.3 and 45.2 mg/kg-d, respectively. PFOA was tolerated in pregnant and lactating dams. There were no PFOA-related effects on pregnancy status, maternal survival, or numbers of dams that delivered pups. There were no differences in body weight of dams throughout gestation and lactation. Minimal decreases (3-4%) in food consumption during some intervals of gestation were seen in both PFOA dose groups; minimal decreases in food consumption during some intervals of lactation (up to 4%) were seen in the high-dose group. There were no differences in postnatal survival in F_1 pups exposed perinatally to PFOA. In the high-dose PFOA group, F_1 pup weights were 5-8% lower than control F_1 pup weights on PNDs 1, 7, 14, and 21.

After PND 21 (i.e., postweaning), F_1 rats were assigned to groups comprising 60 animals/sex. At postweaning females were fed PFOA in the diet at concentrations of 0, 300, or 1,000 ppm which was tolerated for up to 2 years. The perinatal/postweaning PFOA dietary concentrations

in females were as follows: 0/0, 0/300, 0/1,000, 150/300 and 300/1,000 ppm. The resultant average doses in the females not exposed perinatally (0/300 and 0/1,000 ppm) were 18.0 and 63 mg/kg-d and in females exposed perinatally and postnatally (0/0, 150/300, and 300/1,000 ppm) were 0, 18.3 and 63 mg/kg-d (Table 10). At postweaning males were fed PFOA in the diet at concentrations of 0, 150, or 300 ppm. The perinatal/postweaning PFOA dietary concentrations in males were as follows: 0/0, 0/150, 0/300, 150/150, and 300/300 ppm. The resultant average doses in males not exposed perinatally (0/150 and 0/300 ppm) were 13.6 and 27.4 mg/kg-d or exposed perinatally (0/0,150/150, and 300/300 ppm) were 0, 13.6 and 27.6 mg/kg-d. At Week 16 (when the rats were 19 weeks old), 10 rats/sex/group were necropsied; plasma and liver concentrations of PFOA measured. At the same concentration of PFOA in diet (300 ppm), Week 16 mean PFOA plasma concentrations in females were 11- to 12-fold higher than males and Week 16 mean PFOA liver concentrations were 10- to 12-fold higher than males. For each sex, plasma concentrations were similar for groups with the same postweaning PFOA concentration in diet, whether or not the rats were exposed perinatally to PFOA. No tumors were seen at the Week 16 necropsy. Due to decreased body weight (when compared to controls up to 24% and 45% lower at 150 and 300 ppm PFOA in diet, respectively), with concomitant decreased food consumption (when compared to controls up to 13% and 23% lower at 150 and 300 ppm PFOA in diet, respectively), and liver necrosis, the remaining males were terminated at Week 21 (when the rats were 24 weeks old). Therefore, a second study was performed in males dosed for up to 2 years with lower doses of PFOA postweaning.

There were no differences in survival in females exposed to PFOA when compared to the control group. Females in the high-dose groups (0/1000 and 300/1000 ppm) had decreased body weights starting after the first week of dosing postweaning. At the end of the study, females fed 1,000 ppm PFOA in diet during postweaning had mean body weights that were 19% (no perinatal exposure) and 27% (exposed perinatally to high dose of PFOA, correlated with 11% decrease in mean food consumption) lower than controls. In females fed 150/300 ppm PFOA in diet, mean body weights were decreased during the last 4 months of the study; at the end of the study mean body weight was approximately 11% lower than controls. There were no statistically significant differences in tumors in the PFOA groups when compared to controls. Findings in females exposed to PFOA during postweaning only were similar to those seen in females exposed perinatally and during postweaning. Following extended evaluation of uterine tumors and correction of statistics (detailed in NTP revised 2023) uterine adenocarcinomas were increased in the 0/1000 ppm group ($p = 0.05$); this result was considered equivocal and will not be used for derivation of a SFo by TCEQ.

Table 10. Doses and mean plasma concentrations of PFOA in females from NTP (2020, revised 2023)

Diet concentration (perinatal/postweaning)	0/0 ppm	0/300 ppm	0/1,000 ppm	150/300 ppm	300/1,000 ppm
Dose (mg/kg-d)	0	18.0	63	18.3	63
Mean plasma concentration (mg/L) [a]	BD	20.42	72.25	20.80	70.16

a: measured at week 16 (when rats were 19 weeks old)
BD, below detection.

In the second study in which only F_1 males were evaluated, time-mated females were fed PFOA in the diet at concentrations of 0 or 300 ppm. Average doses consumed by the dams in the 300 ppm group during gestation and lactation were 21.8 and 48.3 mg/kg-d, respectively, which was similar to the first study. PFOA was tolerated in pregnant and lactating dams. There were no PFOA-related effects on pregnancy status, maternal survival or numbers of dams that delivered. There were no differences in body weight of dams throughout gestation and lactation. Minimal decreases (≤ 3%) in food consumption during two intervals of gestation were seen in the PFOA group, but food consumption during the entire period of gestation was similar to the control group. Minimal decreases in food consumption (up to 7%) during some intervals of lactation were seen in the PFOA group. There were no differences in postnatal survival in F_1 pups exposed perinatally to PFOA; however, F_1 pup weights were 3-7% lower than control F_1 pup weights on PNDs 1, 4, 7, 14, and 21.

Each group of F_1 rats comprised 60 males. At postweaning F_1 males were fed PFOA in the diet at concentrations of 0, 20, 40 or 80 ppm. Unlike the first study, this second study had a group that was exposed perinatally, but was fed control diet postweaning. The perinatal/postweaning PFOA dietary concentrations in males were as follows: 0/0, 0/20, 0/40, 0/80, 300/0, 300/20, 300/40, and 300/80 ppm. The resultant doses in the males not exposed perinatally (0/0, 0/20, 0/40, 0/80 ppm) were 0, 1.04, 2.18, and 4.49 mg/kg-d (Table 11) and in males exposed perinatally and postnatally (300/0, 300/20, 300/40, and 300/80 ppm) were 0, 1.03, 2.11, and 4.52 mg/kg-d (Table 12). At week 16 (when the rats were 19 weeks old), 10 males/group were necropsied, and plasma and liver concentrations of PFOA were measured. No tumors were seen at the week 16 necropsy. Plasma concentrations of PFOA were similar for groups with the same postweaning PFOA concentration in diet, whether or not the rats were exposed perinatally to PFOA. There were no differences in survival in males exposed to PFOA when compared to the respective control groups. In males exposed during postweaning at concentrations of 20 or 40 ppm PFOA in diet, transient decreases in mean body weight (up to 10%) were seen; however, at the end of the study mean body weights in these groups were similar to those of respective controls. In males exposed during postweaning to 80 ppm PFOA in diet, mean body weights were up to 18% lower than controls during the study; at the end of the study mean body

weights of males in these groups were approximately 9% lower than respective controls. There were no differences in food consumption.

Findings in males exposed to PFOA during postweaning only were similar to those seen in males exposed perinatally and during postweaning (Table 11, Table 12). Note that some males had multiple pancreatic acinar cell adenomas, so the incidences of pancreatic acinar cell adenoma reflect the sum of the incidences of males with one pancreatic acinar cell adenoma and of the incidences of males with multiple pancreatic acinar cell adenomas (Table 11, Table 12). Statistically significant increases in hepatocellular adenoma, and combined hepatocellular adenoma and carcinoma were observed in males in the 0/40 and 0/80 ppm groups, and in males in the 300/80 ppm groups. Additionally, there was a statistically significant dose-response trend for hepatocellular adenoma, and combined hepatocellular adenoma and carcinoma in males. Pancreatic acinar cell adenoma, and combined pancreatic acinar cell adenoma and carcinoma were statistically significantly increased in all PFOA groups when compared to respective controls, with statistically significant dose-response trends for these tumors. Of note, the incidences of hepatocellular and pancreatic acinar cell tumors in the 0/0 and 300/0 ppm groups were all within the range of historical control incidences. Although the oral dose (mg/kg-d) was lower in male rats, the internal dose (plasma concentration) was higher in males than in females. The lack of statistically significant increases in tumors in females exposed to PFOA may be due to the lower internal doses in females when compared to males.

Table 11. Doses, mean plasma concentrations, and tumors in males exposed to PFOA during postweaning only (from NTP 2020, revised 2023)

Diet concentration (perinatal/postweaning)	0/0 ppm	0/20 ppm	0/40 ppm	0/80 ppm
Dose (mg/kg-d)	0	1.04	2.18	4.49
Mean plasma concentration (mg/L) [a]	BD	81.40	130.78	159.60
Hepatocellular adenomas	0/50 [b] (0%) [c]	0/50 (0%)	7/50 (14%)*	11/50 (22%)**
Hepatocellular carcinoma	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
Hepatocellular adenoma and carcinoma, combined	0/50 (0%) [c]	0/50 (0%)	7/50 (14%)*	11/50 (22%)**
Pancreatic acinar cell adenoma	3/50 (6%) [c]	28/50 (56%)***	26/50 (52%)***	32/50 (64%)***
Pancreatic acinar cell adenocarcinoma	0/50 (0%)	3/50 (6%)	1/50 (2%)	3/50 (6%)
Pancreatic acinar cell adenoma and adenocarcinoma combined	3/50 (6%) [c]	29/50 (58%)***	26/50 (52%)***	32/50 (64%)***

a: measured at Week 16 (when rats were 19 weeks old)
b: incidence reported as number of animals with tumor/total number of animals in group
c: $p < 0.001$, trend analysis
BD, below detection.
* $p \leq 0.05$, vs control
** $p \leq 0.01$, vs control
*** $p \leq 0.001$, vs control

Table 12. Doses, mean plasma concentrations, and tumors in males exposed to PFOA perinatally and during postweaning (from NTP 2020, revised 2023)

Diet concentration (perinatal/postweaning)	300/0 ppm	300/20 ppm	300/40 ppm	300/80 ppm
Dose (mg/kg-d)	0	1.03	2.11	4.52
Mean plasma concentration (mg/L) [a]	0.03612	78.03	117.06	144.10
Hepatocellular adenomas	0/50 [b] (0%) [c]	1/50 (2%)	5/50 (10%)	10/50 (20%) **
Hepatocellular carcinoma	0/50 (0%)	0/50 (0%)	0/50 (0%)	4/50 (8%)
Hepatocellular adenoma and carcinoma, combined	0/50 (0%) [c]	1/50 (2%)	5/50 (10%)	12/50 (24%)**
Pancreatic acinar cell adenoma	7/50 (14%) [c]	18/50 (36%)*	30/50 (60%)***	30/50 (60%)***
Pancreatic acinar cell adenocarcinoma	0/50 (0%)	2/50 (4%)	1/50 (2%)	3/50 (6%)
Pancreatic acinar cell adenoma and adenocarcinoma combined	7/50 (14%) [c]	20/50 (40%)**	30/50 (60%)***	30/50 (60%)***

a: measured at Week 16 (when rats were 19 weeks old)
b: incidence reported as number of animals with tumor/total number of animals in group
c: $p < 0.001$, trend analysis
BD, below detection.
* $p \leq 0.05$, vs control
** $p \leq 0.01$, vs control

4.3.2.2.2 Butenhoff et al. (2012a) Oral Carcinogenicity Study

In this study approximately 6-week old Sprague-Dawley rats (Crl:COBS@ CD(SD)BR, Charles River Company, Portage, MI) were fed APFO admixed in the diet at concentrations of 0, 30, or 300 ppm. The mean resultant doses were 1.3 and 14.2 mg/kg-d for males and 1.6 and 16.1 mg/kg-d for females in the 30 and 300 ppm dietary dose groups, respectively. In all groups 50 rats/sex/group were assigned to the 2-year study; in the control and high-dose groups an additional 15 rats/sex/group were terminated at an interim sacrifice at 1-year.

There were no differences in survival in females exposed to APFO when compared to the control group. High-dose males had a statistically significant increase in survival when compared to controls. Mean body weights of high-dose males were decreased (> 10%) through week 66 of the study with the largest decrease of approximately 21% by week 6; this correlated with slight decreases in absolute food consumption during the first year of the study. For the

first 18 months of the study, there were no differences in mean body weights of females; however, at 18 months high-dose females had decreased mean body weights (up to 11% relative to controls) at week 92. Females in both APFO groups had some inconsistent decreases in food consumption; the greatest decrease in food consumption occurred from 18 months to the end of the 2-year study. The authors did not report any tumors at the 1-year interim sacrifice. There were no statistically significant increases in tumors in females exposed to APFO[t]. Males in the high-dose group had a statistically significant increase in Leydig cell tumors of the testes (Table 13).

Table 13. Tumors in male rats exposed to APFO from Butenhoff et al. (2012a)

Diet concentration	0 ppm	30 ppm	300 ppm
Dose (mg/kg-d)	0	1.3	14.2
Testes: Leydig cell adenoma	0/49 [a] (0%)	2/50 (4%)	7/50 (14%) *

a: incidence reported as number of animals with tumor/total number of animals in group
* $p \leq 0.05$, vs control

4.3.2.2.3 Biegel et al. (2001) Oral Carcinogenicity Study

Approximately 6-week old male Crl:CD® BR (CD) Sprague Dawley rats (Charles River Laboratories, [Raleigh, NC]) were fed PFOA in diet at concentrations of 0 or 300 ppm, with resultant doses of 0 and 13.6 mg/kg-d. There were two control groups: one fed ad libitum and one that was pair-fed to the PFOA group (i.e., fed the same amount of diet consumed by the PFOA group). Each group comprised 156 rats/group. Interim sacrifices were performed and, therefore, up to 80 rats/group were available for the main carcinogenicity part of the study. From Days 8 to 630, body weights were decreased in the pair-fed and PFOA groups when compared to the ad libitum group. On Day 714, survival was increased in the pair-fed and PFOA groups. When compared to the pair-fed control group, statistically significant increases in hepatocellular adenoma, combined hepatocellular adenoma and carcinoma, and combined pancreatic acinar cell adenoma and carcinoma were seen in the PFOA group. Additionally, a

[t] In Butenhoff et al. (2012a) it is documented that the mammary gland tissues from female rats were subjected to a blinded pathology peer review using updated toxicological pathology criteria (Hardisty et al. 2010). This resulted is a different distribution of mammary gland tumor incidences. Both the original and peer review results are presented in Table 8 in Butenhoff et al. (2012a). The principal difference between the original reported findings and the pathology working group results involved changes in the mammary gland that were initially reported as lobular hyperplasia, which the pathology working group thought had features more characteristic of mammary gland fibroadenoma. As a result, the numbers of rats with benign tumors (adenoma and fibroadenoma) were reclassified in all groups, including the control group. Although the incidence of neoplasms varied among the control and the APFO groups, there were no statistically significant differences when evaluated using the Fisher's exact test for pairwise comparison for fibroadenoma, adenocarcinoma, total benign neoplasms, and total malignant neoplasms. The morphologic appearance, overall incidence, and distribution of the neoplasms observed in APFO and control groups were similar.

statistically significantly increased incidence of Leydig cell adenoma of the testes was seen in the PFOA group when compared to the ad libitum group (Table 14).

Table 14. Tumors in male rats exposed to PFOA from Biegel et al. (2001)

Diet concentration (ppm)	0 (ad libitum)	0 (pair-fed)	300
Dose (mg/kg-d)	0	0	13.6
Hepatocellular adenoma	2/80 [a] (3%)	1/79 (1%)	10/76 (13%) [b]
Hepatocellular carcinoma	0/80 (0%)	2/79 (3%)	0/76 (0%)
Hepatocellular adenoma and carcinoma, combined	2/80 (3%)	3/79 (4%)	10/76 (13%) [b]
Pancreatic acinar cell adenoma	0/80 (0%)	1/79 (1%)	7/76 (9%) [b]
Pancreatic acinar cell adenocarcinoma	0/80 (0%)	0/79 (0%)	1/76 (1%)
Pancreatic acinar cell adenoma and adenocarcinoma combined	0/80 (0%)	1/79 (1%)	8/76 (11%) [b]
Testes: Leydig cell adenoma	0/80 (0%)	2/78 (3%)	8/76 (11%) [c]

a: incidence reported as number of animals with tumor/total number of animals in group
b: $p < 0.05$, vs pair-fed control
c: $p < 0.05$, vs ad libitum control

4.3.3 Carcinogenic MOA for PFOA

As described in Section 3.5.3.1.1 of USEPA (2024a), most of the studies assessing mutagenicity following PFOA exposure have been negative. Therefore, there is a lack of evidence of a mutagenic MOA, and USEPA deems it unlikely that PFOA causes tumorigenesis via a mutagenic MOA (p. 4-73 of USEPA 2024a). Regarding other MOAs, Section 3.5.4.2.3 of USEPA (2024a) indicates that two proposed MOAs for PFOA-induced pancreatic tumors in animal models, the endpoint utilized by TCEQ below, were identified in the literature, including one study that utilizes a transgenic mouse model to mimic the histologic progression of pancreatic cancer in humans (Kamendulis et al. 2022, Klaunig et al. 2003, 2012). The proposed MOAs are: 1) changes in bile acids, potentially linked to activation of hepatic PPARα, leading to cholestasis, a positive cholecystokinin (CCK) feedback loop, and acinar cell proliferation; and 2) oxidative stress. However, the existing database is limited in its ability to determine the relationship between PFOA exposure and these MOAs, particularly for the pancreatic acinar cell tumors observed in

chronic rat studies. Ultimately, USEPA (2024a) concludes regarding the MOAs for the pancreatic tumors that:

> Overall, due to limited evidence for altered bile flow in animals that developed tumors and an overall lack of evidence for alterations in CCK levels in PFOA-exposed animals, there is not sufficient evidence to determine whether bile acid alterations contribute to the MOA for pancreatic acinar cell tumors observed in rodents chronically exposed to PFOA; and, although plausible, there is not sufficient evidence for key events related to an oxidative stress MOA to conclude that the pancreatic tumors in rodents chronically exposed to PFOA are the result of oxidative stress and related molecular events.

Thus, the carcinogenic MOA remains unknown for the rat pancreatic tumors ultimately serving as the critical endpoint for TCEQ's PFOA SFo (see below). Generally, linear low-dose extrapolation is the extrapolation method used to derive cancer-based toxicity factors (e.g., SFo) for chemicals with an unknown carcinogenic MOA (TCEQ 2015).

4.3.4 Selection of the Key Study and Critical Effect for PFOA

Table 4-13 of USEPA (2024a) contains candidate PFOA SFo values based on 2-year studies in Sprague Dawley rats. Note that one of these studies (NTP 2020, revised 2023) included prenatal and postnatal exposure (referred to as perinatal exposure in the report) via dosing of dams during gestation and lactation, respectively. USEPA modeled the tumor data using BMDS 3.2 and stated that for cancer endpoints, multistage models are generally preferred (USEPA 2024a, Section E.1) and cited the USEPA's benchmark dose technical guidance (USEPA 2012). Therefore, the results presented in USEPA (2024a) only show results of multistage models. TCEQ also modeled the tumor data using BMDS online 25.1 and taking into consideration all models with $p > 0.1$, the absolute value of scaled residuals < 2, viable models with BMDL within 3-fold, and the lowest AIC, the results shown in Table 4-13 of USEPA (2024a, reproduced below) were the same or similar to those selected by USEPA. Note that USEPA uses the term CSF (cancer slope factor) and TCEQ uses the term SFo (oral slope factor); these toxicity factors are the same.

Table 4-13. Candidate Cancer Slope Factors Based on Animal Toxicological Data from 2-year Cancer Bioassays

Tumor Type	Reference, Confidence	Strain/ Species/Sex	POD Type, Model	POD Internal Dose/Internal Dose Metric*	POD_{HED}	CSF (BMR/POD_{HED})	Notes on Model Selection
Leydig Cell Adenomas in the Testes	Butenhoff et al. (2012) *Medium*	Male Sprague-Dawley Rats	$BMDL_{4RD}$, Multistage Degree 1	27,089.3 AUC_{avg} (mg × d/L)	4.75×10^{-3} mg/kg/day	8.42 $(mg/kg/day)^{-1}$	Model selected based on lowest AIC as all models had adequate fit and BMDLs were within sufficiently close.
Hepatocellular Adenomas or Carcinoma	NTP (2020) *High*	F_1 Male Sprague-Dawley Rats, Perinatal and Postweaning Exposure	$BMDL_{10RD}$, Multistage Degree 2	88.7 ($C_{avg\_pup\_total}$ in mg/L)	1.06×10^{-2} mg/kg/day	9.4 $(mg/kg/day)^{-1}$	Model selected based on lowest AIC as all models had adequate fit and BMDLs were within sufficiently close.
Hepatocellular Adenomas	NTP (2020) *High*	F_1 Male Sprague-Dawley Rats, Perinatal and Postweaning Exposure	$BMDL_{10RD}$, Multistage Degree 2	93.0 ($C_{avg\_pup\_total}$ in mg/L)	1.12×10^{-2} mg/kg/day	9.0 $(mg/kg/day)^{-1}$	Model selected based on lowest AIC as all models had adequate fit and BMDLs were within sufficiently close.
Pancreatic Acinar Cell Adenoma or Adenocarcinoma	NTP (2020) *High*	F_1 Male Sprague-Dawley Rats, Perinatal and Postweaning Exposure	$BMDL_{10RD}$, Multistage Degree 3	15.2 ($C_{avg\_pup\_total}$ in mg/L)	1.83×10^{-3}	54.7 $(mg/kg/day)^{-1}$	Model selected based on lowest AIC as all models had adequate fit and BMDLs were within sufficiently close.
Pancreatic Acinar Cell Adenoma	NTP (2020) *High*	F_1 Male Sprague-Dawley Rats, Perinatal and Postweaning Exposure	$BMDL_{10RD}$, Multistage Degree 1	15.7 ($C_{avg\_pup\_total}$ in mg/L)	1.88×10^{-3}	53.2 $(mg/kg/day)^{-1}$	Model selected based on lowest AIC as all models had adequate fit and BMDLs were within sufficiently close.

Notes: AUC = area under the curve; $BMDL_{4RD}$ = benchmark dose level corresponding to the 95% lower confidence limit of a 4% change; $BMDL_{10RD}$ = lower bound on the dose level corresponding to the 95% lower confidence limit for a 10% change; BMR = benchmark response; CSF = cancer slope factor; NTP = National Toxicology Program.
* See Appendix (U.S. EPA, 2024a) for additional details on benchmark dose modeling.

Most of the candidate values are based on NTP (2020, revised 2023), a high confidence study that also provided the most conservative SFo values based on animal studies. For example, per TCEQ's data extraction during systematic review, the lowest LOAEL for cancer effects in NTP (2020, revised 2023) is 1 mg/kg-d (corresponding to perinatal/postweaning dietary doses of 300/20 ppm) based on either pancreatic acinar cell adenoma, or pancreatic acinar cell adenoma or adenocarcinoma (combined) in male SD rats.

In two studies (NTP 2020, revised 2023 and Biegel et al. 2001) there were statistically significant increases in pancreatic acinar cell adenomas in male SD rats only. It is important to note that there were no statistically significant increases in pancreatic acinar cell adenocarcinoma in all three carcinogenicity studies in both sexes, and that the statistically significant increase in combined pancreatic acinar cell adenoma and adenocarcinoma in male SD rats was driven by the incidences of pancreatic acinar cell adenomas. These pancreatic tumors, based on results from NTP (2020, revised 2023), provide the highest candidate PFOA SFo values in Table 4-13 of USEPA (2024a) and are considered further below for adoption by TCEQ as critical effects (i.e., the most sensitive carcinogenic effects considered for laboratory animals) for the carcinogenic dose-response assessment.

4.3.5 Adjustments to the POD

4.3.5.1 BMD Modeling

For carcinogenic dose-response assessment, the data should be adequate to characterize the dose-response curve (TCEQ 2015). For pancreatic acinar cell adenoma or adenocarcinoma in male SD rats from NTP (2020, revised 2023), it is noted that the data at the low doses of particular interest for regulatory environmental risk assessment and SFo derivation (72.6 and 73.6 mg/L serum from Table E-86 of USEPA 2024a below) suggest excess risk. A BMR of 10% extra risk was chosen per EPA's Benchmark Dose Technical Guidance (USEPA 2012). The internal dose represents the average PFOA plasma concentration in pups from conception to the end of the 2 years. Specifically, it is the sum of the area under the curve (AUC) from exposure during gestation and lactation and the AUC from exposure to consuming PFOA in the diet (postweaning) divided by 2 years.

Table E-86. Dose-Response Modeling Data for Pancreatic Acinar Cell Adenoma or Adenocarcinoma (Combined) in F_1 Male Sprague-Dawley Rats Following Exposure to PFOA (NTP, 2020)

Administered Dose (ppm)[a]	Internal Dose (mg/L)	Number per Group	Incidence
0 / 0	0	50	3
300 / 0	0.4	50	7
0 / 20	72.6	50	29
300 / 20	73.6	50	20
0 / 40	113.5	50	26
300 / 40	115.2	50	30
0 / 80	161.7	50	32
300 / 80	161.8	50	30

Notes:
[a]Doses are presented as perinatal exposure/postnatal exposure.

Upon visual inspection, USEPA's selected BMD model curve seems to adequately reflect these data, including the lower doses. See Figure E-23 and Table E-87 (reproduced below) from USEPA (2024a).

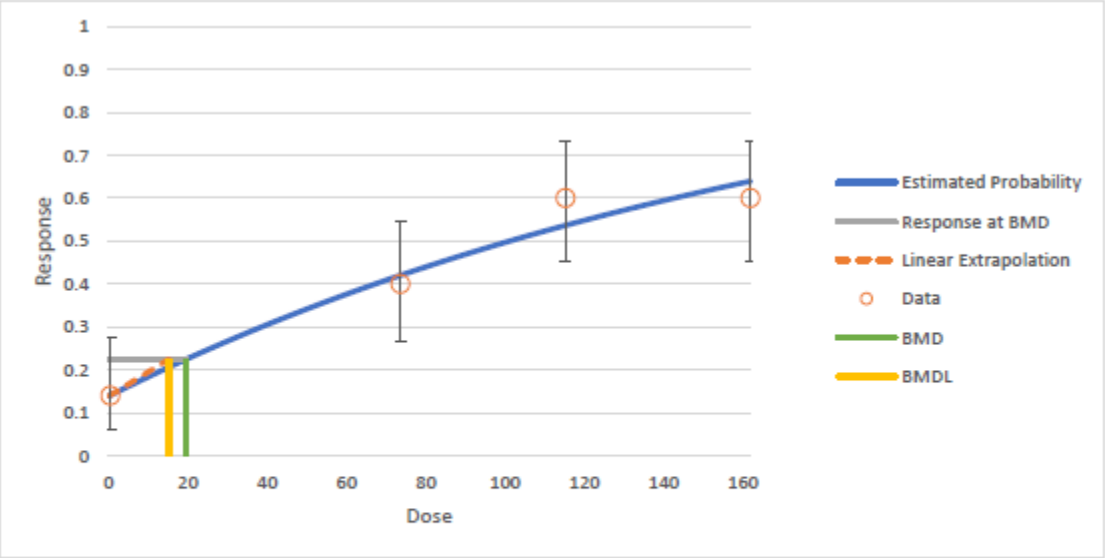

Figure E-23. Plot of Incidence Rate by Dose with Fitted Curve for the Selected Multistage Degree 3 Model Pancreatic Acinar Cell Adenoma or Adenocarcinoma in F_1 Male Sprague-Dawley Rats Following Perinatal and Postweaning Exposure to PFOA (NTP, 2020)

BMD = benchmark dose; BMDL = benchmark dose lower limit.

Table E-87. Summary of Benchmark Dose Modeling Results for Pancreatic Acinar Cell Adenoma or Adenocarcinoma in F_1 Male Sprague-Dawley Rats Following Perinatal and Postweaning Exposure to PFOA (NTP, 2020)

Model[a]	Goodness of Fit		Scaled Residual		BMD_{10} (mg/L)	$BMDL_{10}$ (mg/L)	Basis for Model Selection
	p-value	AIC	Dose Group Near BMD	Control Dose Group			
Multistage Degree 3	**0.541**	**247.6**	**–0.02**	**–0.02**	**19.6**	**15.2**	EPA selected the Multistage Degree 3 model. All models had adequate fit (p-values greater than 0.1), and the BMDLs were sufficiently close (less than threefold difference), and the Multistage Degree 3 model had the lowest AIC.
Multistage Degree 2	0.541	247.6	–0.02	–0.02	19.6	15.2	
Multistage Degree 1	0.541	247.6	–0.02	–0.02	19.6	15.2	

Notes: AIC = Akaike information criterion; BMD = benchmark dose; BMDL = benchmark dose lower limit; BMD_{10} = dose level corresponding to a 10% response level; $BMDL_{10}$ = lower bound on the dose level corresponding to the 95% lower confidence limit for a 10% response level.
[a] Selected model in bold.

Based on the considerations discussed above (e.g., most sensitive laboratory animal carcinogenic endpoint considered, adequate BMD model fit), TCEQ chose the corresponding benchmark dose lower confidence limit at a 10% response $BMDL_{10}$ of 15.2 mg/L serum (Tables 4-13 and E-87 of USEPA 2024a) as the animal $POD_{Internal}$ for derivation of the TCEQ SFo for PFOA.

4.3.5.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

As in USEPA (2024a), the animal $POD_{Internal}$ of interest can be converted to the corresponding $POD_{HED\text{-}oral}$ by multiplying the animal $POD_{Internal}$ by the human clearance value. For this conversion, TCEQ utilized the geometric mean (GM) human clearance of 0.00012 L/kg-d (Table 4-6 in USEPA 2024a). The animal $POD_{Internal}$ based on the most sensitive endpoint (i.e., pancreatic acinar cell adenoma or adenocarcinoma) from Table 4-13 in USEPA (2024a) is 15.2 mg/L. Thus, the corresponding POD_{HED} is calculated as:

$$POD_{HED\text{-}oral} = POD_{Internal} \text{ of } 15.2 \text{ mg/L} \times 0.00012 \text{ L/kg-d} = 0.0018 \text{ mg/kg-d}$$

This POD_{HED} of 1.8E-03 mg/kg-d was used for derivation of TCEQ's PFOA SFo.

4.3.6 Calculation of an Oral Slope Factor

The SFo for PFOA is calculated as:

$$SFo = BMR/ POD_{HED} = 0.1/1.8E\text{-}03 \text{ mg/kg-d} = \mathbf{54.7 \text{ per mg/kg-d}}$$

Thus, the SFo for PFOA rounded to two significant figures is 55 per mg/kg-d, based on the most sensitive effect from NTP (2020, revised 2023), pancreatic acinar cell adenoma or adenocarcinoma in male SD rats. Accordingly, the PFOA SFo of 55 per mg/kg-d is selected by TCEQ.

4.3.7 Comparison of Cancer Potency Factors

TCEQ considers the PFOA SFo of 55 per mg/kg-d to be sufficiently health protective and conservative considering:

- The laboratory animal database and selection of the more sensitive sex (male SD rats) in conjunction with the most sensitive endpoint in Table 4-13 of USEPA (2024a); and
- Use of the lower statistical bound on the dose (i.e., $BMDL_{10}$).

The significant limitations/weaknesses of the epidemiological database and the unrealistic cancer risk estimates that result from application of USEPA's epidemiology-based SFo (0.0293 per ng/kg-d; USEPA 2024a) to NHANES biomonitoring results for PFOA in the U.S. general population are discussed in Appendix 6.

4.3.8 Evaluating Susceptibility from Early-Life Exposures

In the absence of chemical-specific data on the potential greater susceptibility of children (or young animals of other species) to the potential carcinogenic effects of the chemical in question, USEPA (2005b) provides default age-dependent adjustment factors (ADAFs) to account for potentially increased susceptibility in children due to early-life exposure when a chemical has been identified as acting through a mutagenic MOA for carcinogenicity. As discussed in Section 4.2.4 of USEPA (2024a), most of the studies assessing mutagenicity following PFOA exposure have been negative and therefore, PFOA is unlikely to cause tumorigenesis via a mutagenic MOA. Given the lack of evidence of a mutagenic MOA, USEPA did not recommend applying ADAFs when quantitatively estimating PFOA cancer risk. Additionally, the chronic NTP (2020, revised 2023) PFOA rat study utilized by TCEQ for the SFo was designed to assess the contribution of combined gestational and lactational exposure (referred to as perinatal exposure) to the chronic carcinogenicity of PFOA (NTP 2020). That is, the study that TCEQ relied upon (NTP 2020, revised 2023) incorporated both perinatal and postweaning exposure, so the extent to which young animals had greater susceptibility is reflected in the dose-response data. Regarding this, USEPA (2024a) indicates that in this 2-year NTP cancer bioassay in rats chronically exposed to PFOA both perinatally and postweaning, an increased cancer risk compared with chronic postweaning-only exposure was not reported (p. 4-74 of USEPA 2024a, also refer to NTP 2020, revised 2023). This suggests no increased cancer risk as a result of lifetime, including perinatal, exposure compared with postweaning-only exposure (i.e., there was a lack of evidence supporting early-life susceptibility to PFOA exposure).

Consistent with the discussion above, for these reasons (i.e., the lack of data adequately supporting a mutagenic MOA for carcinogenicity, reliance on a study that assessed cancer after including PFOA exposure during development), ADAFs are not applied to the TCEQ SFo for PFOA. Again, this is consistent with USEPA (2024a), which did not recommend applying ADAFs when quantitatively determining the cancer risk for PFOA (p. 4-73 of USEPA 2024a).

4.3.9 Chronic Carcinogenic OAEL for PFOA

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, 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 carcinogenic OAEL is provided for informational purposes only (TCEQ 2015).

The lowest carcinogenic $POD_{HED\text{-}oral}$ for PFOA was 0.00183 mg/kg-d for combined pancreatic acinar cell adenoma and carcinoma in male SD rats exposed perinatally and postweaning for a

total of 107 weeks (see Section 4.3.4 wherein the candidate PODs from USEPA 2024a are shown). Therefore, the OAEL for PFOA is set at 0.00183 mg/kg-d.

The SFo that results from linear low-dose extrapolation below the range of the data is 55 per mg/kg-d. The extrapolated dose of PFOA for a theoretical excess risk of 1 in 100,000 is 1.8E-07 mg/kg-d. The MOE between the carcinogenic OEAL (0.00183 mg/kg-d) and the extrapolated dose of PFOA for an excess risk of 1 in 100,000 (1.8E-07 mg/kg-d) is a factor of 10,065.

4.4 Carcinogenic Weight of Evidence for PFOS

TCEQ determined that the designation of "likely to be carcinogenic to humans" for PFOS is not supported by the data, and therefore, it is inappropriate to derive an SFo for PFOS. Moreover, for PFOS the mechanistic evidence for cancer is relatively nonspecific, may be observed with non-carcinogenic agents, and is not considered strong.

USEPA has designated PFOS as "likely to be carcinogenic to humans" based on mostly null or limited evidence of associations with various cancers in epidemiology studies and on one chronic study in rats in which a weak tumor response was observed. Of note, the International Agency for Research on Cancer (IARC) has designated PFOS as "possibly carcinogenic to humans (Group 2B)" on the basis of "strong mechanistic evidence", but limited evidence for cancer in experimental animals and inadequate evidence for cancer in humans for PFOS (Zahm et al. 2024). The mechanistic evidence described by IARC was based on what have been labeled as the key characteristics of carcinogens, which provide an approach to evaluate mechanistic evidence for cancer hazard identification (Smith et al. 2016). These key characteristics are described as chemical and biological properties of known carcinogens, and were also used by USEPA in the carcinogenic hazard assessment for PFOS. However, some of these key characteristics are not evidence-based and may be seen with chemicals that are not carcinogens (e.g., oxidative stress, chronic inflammation, modulation of receptor-mediated effects, microRNA expression). These characteristics may be useful in organizing the MOA for an agent that may be a carcinogen, but when used alone they have limited utility in distinguishing between carcinogenic and non-carcinogenic agents. The mechanistic evidence is considered to be supporting information, and the epidemiological and animal toxicity data should take precedence in hazard evaluation of a potential carcinogen.

Regarding the mechanistic evidence, PFOS is not a mutagen and is not genotoxic. PFOS is not an electrophilic molecule and is not metabolized, and therefore cannot be metabolized to an electrophilic molecule. PFOS has not been shown to alter DNA repair or cause genomic instability, or cause immortalization of cells in culture (USEPA 2024b).

USEPA's Human Health Toxicity Assessment for PFOS (USEPA 2024b; pp. 3-262 to 3-264) mentions that in the previous review of epidemiology studies available prior to 2016, seven

epidemiology studies were available from human populations, including occupational cohorts, community participants as part of the C8 project, and general populations. Overall, USEPA concluded that there was no evidence of carcinogenic effects for PFOS in these studies.

Since 2016, seventeen additional epidemiology studies were published that evaluated associations between PFOS exposure and cancer (USEPA 2024; pp. 3-265 to 3-269). Two studies (Li et al. 2022, Wielsøe et al. 2017) were considered uninformative because of concerns about exposure assessment, lack of data on important covariates, and/or participant selection, and were not considered further. One study (Lin et al. 2020), considered to be of low confidence, showed mixed results in associations between PFOS and germ cell tumors in children. In a nested case control study in the US general population (Shearer et al. 2021) a statistically significant positive trend in risk of renal cell carcinoma with pre-diagnostic serum levels of PFOS was reported; however, the effect in the third quartile was null and after adjustment for other PFAS there was no significant effect. In addition, seven general population studies evaluated PFOS and risk for breast cancer with mixed results. Three studies (Itoh et al. 2021, Omoike et al. 2021, Tsai et al. 2020) were considered to be of low confidence due to concerns about exposure measurements that did not pre-date breast cancer development, lack of confirmation of control status via examination or medical records (Omoike et al. 2021, Tsai et al. 2020), and/or potential for residual confounding due to socioeconomic status, lifestyle factors, and exposure to other PFAS. These three studies showed mixed or inverse relationships between PFOS exposure and breast cancer. In the remaining studies assessing potential risk for breast cancer, one nested case-control study did not observe an association between breast cancer (identified through the California cancer registry) and PFOS concentrations in serum after case diagnosis (maximum serum concentration of PFOS was 99.8 ng/mL) (Hurley et al. 2018); one nested case-control study in a prospective (pregnancy) cohort study (the Child Health and Development Studies) suggested that maternal PFOS was associated with a decrease in the daughters' breast cancer risk in the first or fourth quartile (Cohn et al. 2020); and two nested case control studies with a small number of cases (Ghisari et al. 2017, Mancini et al. 2020) showed limited associations with breast cancer.

Two epidemiology studies evaluated associations with liver cancer. One study (Cao et al. 2022) was considered to be of low confidence due to limited or lack of information regarding selection of controls, diagnosis method for liver cancer, adjustment for potential confounding, and details of the statistical analysis. The other study (Goodrich et al. 2022) was a small, nested case control study of US adults (50 cases and 50 controls) in which participants with PFOS exposures above the 85th percentile (54.9 ng/mL) had an increased risk of liver cancer; however, the association was no longer statistically significant in analyses of continuous exposure.

One study based on the C8 Health Project (Ducatman et al. 2015) examined prostate-specific antigen as a biomarker for prostate cancer in adult males who lived, worked, or went to school in water districts contaminated by the DuPont Washington Works facility. No association was observed between prostate specific antigen levels and PFOS serum concentrations. Omoike et al. (2021) observed an inverse association between PFOS exposure and prostate cancer or uterine cancer in an NHANES population study; results for ovarian cancer were mixed. In a study considered to be of low confidence (Liu et al. 2021) serum PFOS exposure was inversely associated with thyroid cancer.

Lastly, two studies examined all cancer types together. In Fry and Power (2017) there was no association of cancer mortality with PFOS exposure in participants over 60 years of age from NHANES. In Christensen et al. (2016) PFOS exposure was not associated with self-reported cancer incidence in male anglers over 50 years of age.

Overall, the weight of evidence from epidemiology studies does not show a consistent pattern of increased risk or association between cancer and PFOS exposure.

A single chronic animal study is available that evaluated the potential for carcinogenicity. In this chronic study, approximately 6-week old Sprague Dawley rats (Crl:CD®(SD)IGS BR, Charles River Laboratories, [Raleigh, NC]) were fed potassium perfluorooctane sulfonate in diet for up to 2 years at concentrations of 0, 0.5, 2, 5, or 20 ppm (Butenhoff et al. 2012b). The final mean doses were 0, 0.024, 0.098, 0.242, and 0.984 mg/kg-d in males and 0, 0.029, 0.120, 0.299, and 1.251 mg/kg-d in females. Survival in males in the 0.242 and 0.984 mg/kg-d groups were statistically significantly higher than the control group.

Statistical analyses of tumor data were performed separately by the study authors (Butenhoff et al. 2012b) and by USEPA (USEPA 2024b, Table 3-18). Of note, USEPA reported the number of tumors as a percent of the number of animals alive at the time of first occurrence of the tumor; Butenhoff et al. (2012b) reported the number of tumors as a percent of the total number of animals per group. Reporting the incidence based on the number of animals alive at the time of first occurrence of tumor inflates the percentage of animals with tumors, compared to using the total number of animals per group.

In the statistical analyses performed by both USEPA (2024b) and Butenhoff et al. (2012b) there was a statistically significant increase in hepatocellular adenomas in males at the high-dose of 0.984 mg/kg-d, with a significant trend. In females a statistically significant increase in hepatocellular adenomas, and in hepatocellular adenomas and carcinomas (combined) at the high-dose of 1.251 mg/kg-d was observed. In males and females no hepatocellular tumors were observed in the controls. The incidence of hepatocellular adenomas in the high-dose males and females was relatively low, and one hepatocellular carcinoma was seen in one high-dose female only (one out of 540 rats total in the study, equal to an incidence of 0.2%). Although not

reported in the Butenhoff et al. (2012b) paper, USEPA reported the incidences of pancreatic islet cell tumors in males from the 2-year study (USEPA 2024b, Table 3-18). USEPA reported that in males there was a statistically significant trend for pancreatic islet cell carcinomas, but no statistically significant differences in any dose group versus control. There were no statistically significant differences in pancreatic islet cell adenomas, and combined pancreatic islet cell adenomas and carcinomas, in males.

Overall, the tumor response was weak in Butenhoff et al. (2012b). When one takes into account the historical control data of 104-wk studies conducted in the same strain and source of rat, in the time frame that is close to when the study was conducted (2001 to 2009) (Giknis and Clifford 2013), the tumors that were seen at incidences above the historical control data range were the hepatocellular adenomas and pancreatic islet cell carcinomas in males only. Of note, survival in males in the two highest dose groups was statistically significantly greater than that of controls, allowing more time for tumors to develop. Females did have statistically significant increases in hepatocellular adenomas, but the highest incidence, which occurred in the high-dose group, was within the range of the historical control data. The statistically significant trend and findings at high doses were likely driven by the uncommon absence of hepatocellular tumors in the concurrent controls in males and females.

Activation of nuclear receptors (peroxisome proliferator activated receptor α [PPARα], constitutive androstane receptor [CAR], and pregnane X receptor [PXR]) is believed to be the mode of action for PFOS-induced formation of liver tumors in rats. It is not clear that this mode of action of liver tumor formation occurs in humans. Based on the epidemiology studies, there is no correlation between the tumors observed in rats and evidence of cancer, including risk for liver or pancreatic cancer, in humans.

In conclusion, the single chronic study in rats shows: (1) a relatively weak positive tumor response in one species; (2) statistically significant findings in hepatocellular tumors driven by absence of hepatocellular tumors in concurrent control males and females; (3) all hepatocellular tumors were benign except for one hepatocellular carcinoma observed in one rat that could be due to chance; and (4) a statistically significant trend for increased pancreatic islet cell carcinomas was observed in males only, but these tumors were not statistically significantly increased when combined with pancreatic islet cell adenomas.

When taken together, the mostly null evidence for cancer in epidemiology studies (24 total evaluated by USEPA) and the weak tumor response in the single chronic study conducted in one animal species does not support USEPA's hazard identification for PFOS of "likely carcinogenic to humans". Instead, similar to the designation from IARC, TCEQ has determined that a hazard identification for PFOS of "possibly carcinogenic to humans", based on limited evidence for cancer in experimental animals and inadequate evidence for cancer in humans, is more appropriate.

Based on the current evidence, TCEQ will adopt the same hazard identification for PFOS as IARC, “possibly carcinogenic to humans (Group 2B)”. TCEQ only derives cancer slope factors for chemicals that are carcinogenic to humans or likely to be carcinogenic to humans (TCEQ 2015). Because TCEQ will adopt the same carcinogenic classification as IARC based on limited evidence for cancer in experimental animals and inadequate evidence for cancer in humans, TCEQ will not derive a SFo. If new significant evidence for the potential for carcinogenicity becomes available for PFOS, then TCEQ will review and determine whether there is enough evidence to revise the hazard identification to “carcinogenic to humans” or “likely carcinogenic to humans”, and will derive a SFo if the data are amenable to a derivation.

4.5 Summary of the Chronic Values

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

- **RfD for PFOA**: 2.2E-05 mg/kg-d for PFOA, 2.3E-05 mg/kg-d for APFO and sodium perfluorooctanoate, and 2.4E-05 mg/kg-d for potassium perfluorooctanoate
- **RfD for PFOS**: 2.9E-05 mg/kg-d for PFOS, 3.0E-05 mg/kg-d for ammonium perfluorooctanesulfonate and sodium perfluorooctanesulfonate, and 3.2E-05 mg/kg-d for potassium perfluorooctanesulfonate
- **SFo for PFOA** = 55 per mg/kg-d for PFOA, 53 per mg/kg-d for APFO and sodium perfluorooctanoate, and 51 per mg/kg-d for potassium perfluorooctanoate

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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 PFOA and PFOS, the number of references at this stage of screening were 1,538 and 1,446, respectively. The full text of the references included after categorization was further screened. Following full text review there were 110 animal toxicity studies and 16 epidemiology studies that were included for PFOA, and 106 animal toxicity studies and 1 epidemiology study that were included for PFOS. Data extraction and study quality evaluation were conducted for each of these PFOA and PFOS 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 PFOA and PFOS. Further information can be found in TCEQ (2025).

Appendix 2 MPPD Program Outputs

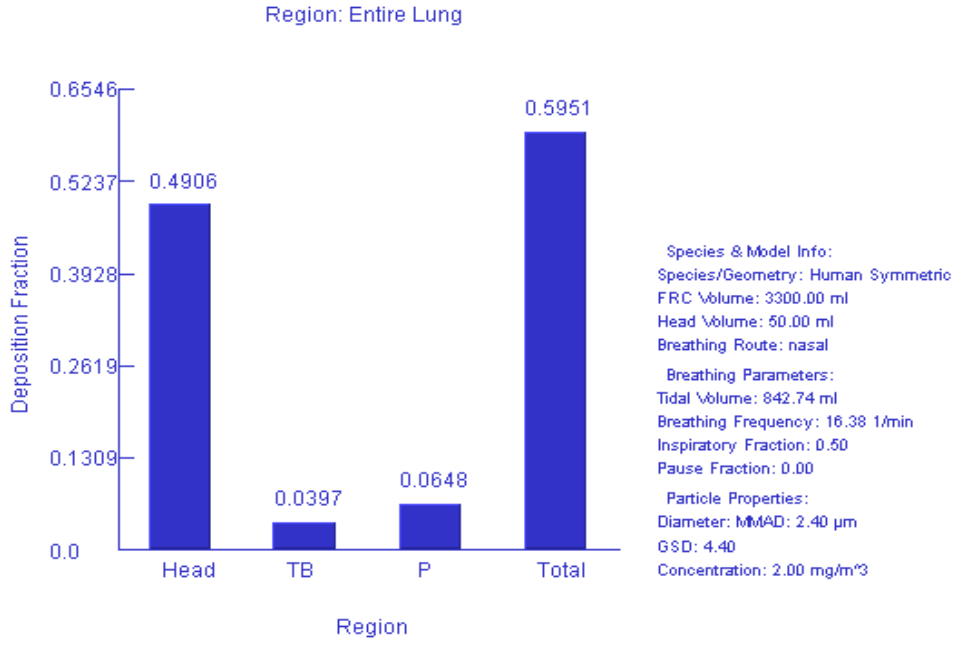

Figure 1 Human output from the MPPD model for key study (Staples et al., 1984)

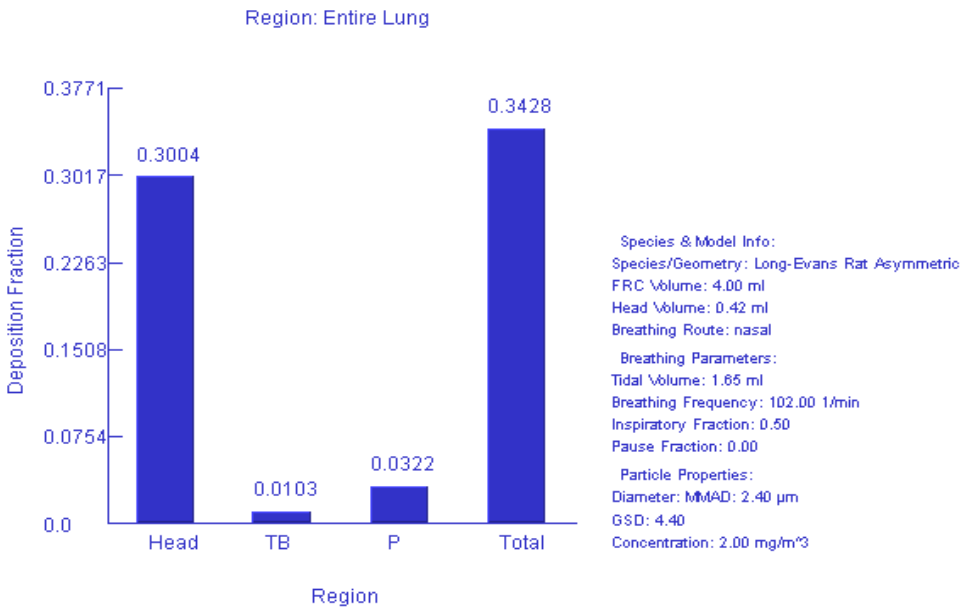

Figure 2 Rat output from the MPPD model for key study (Staples et al., 1984)

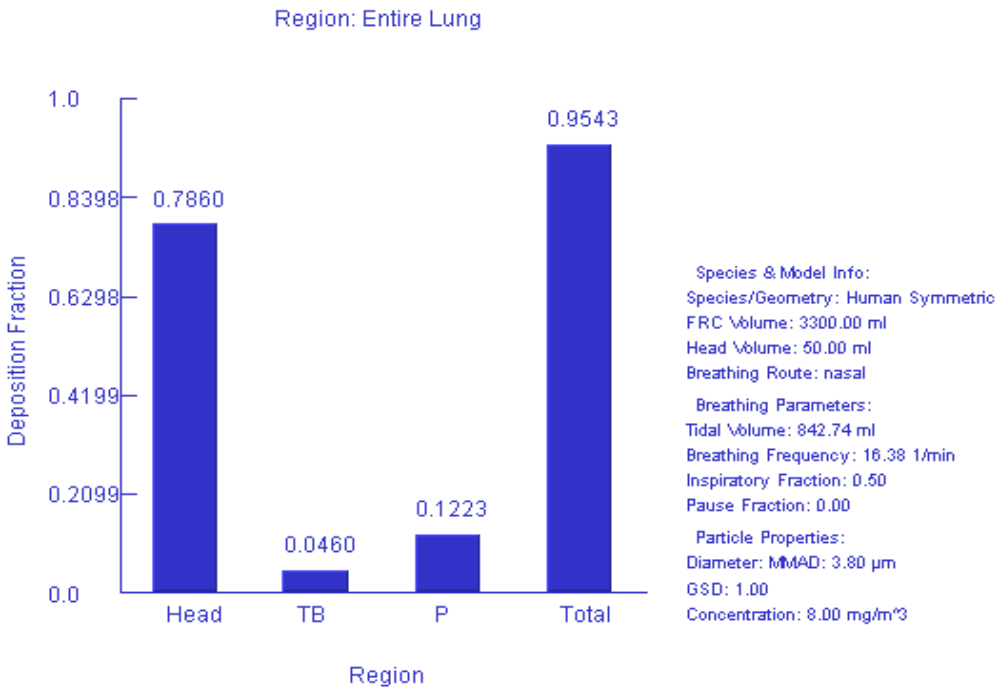

Figure 3 Human output from the MPPD model for supporting study (Kennedy et al., 1986)

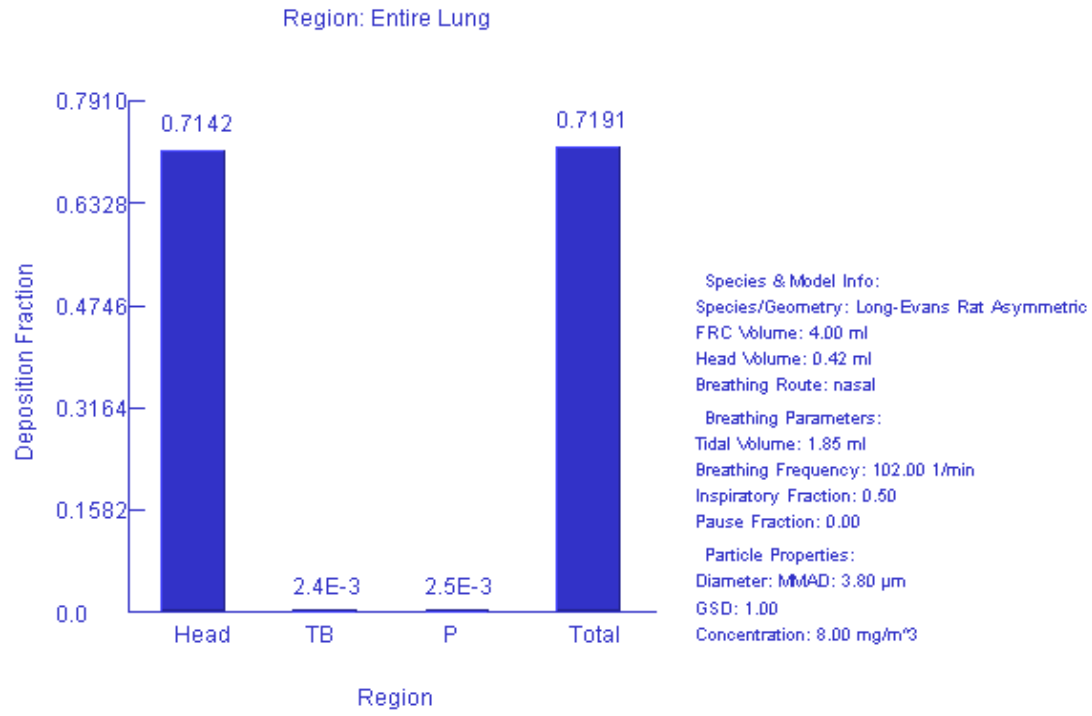

Figure 4 Rat output from the MPPD model for supporting study (Kennedy et al., 1986)

Appendix 3 Reference Doses for PFOA and PFOS Derived by USEPA

TCEQ determined that epidemiologic studies are insufficient for dose-response assessment and derivation of reference doses for PFOA and PFOS.

USEPA derived the following RfDs for PFOA and PFOS (Table 15) (USEPA 2024a, USEPA 2024b), based on epidemiological studies.

Table 15. Reference Doses for PFOA and PFOS Derived by USEPA

Chemical	RfD	Critical Effect(s), Critical Study/Studies
PFOA	3×10^{-8} mg/kg-d	Reduced antibody response to vaccinations in children (diphtheria and tetanus) (Budtz-Jørgensen and Grandjean, 2018); decreased birth weight in infants (Wikström et al., 2020); increased serum total cholesterol in adults (Dong et al., 2019)
PFOS	1×10^{-7} mg/kg-d	Decreased birth weight in infants (Wikström et al., 2020); increased serum total cholesterol in adults (Dong et al., 2019)

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

While the epidemiology data may be appropriate for hazard identification TCEQ believes that, due to weaknesses and limitations of the epidemiological study evidence, the associated epidemiologic results (e.g., immunotoxicity, decreased birth weight, and increased serum total cholesterol) are not sufficient for quantitative risk assessment and toxicity factor (e.g., RfD) derivation for PFOA and PFOS. 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 (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 different epidemiology-based critical effects selected for RfD derivation for PFOA and/or PFOS (antibody responses to vaccination, decreased birth weight, and serum cholesterol) 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 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 the basis of the RfD for PFOA.

In their October 2024 Public Consultation Draft for Per- and Poly-Fluoroalkyl Substances (PFAS), the Australian Government's National Health and Medical Research Council[u] (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. Specifically, TCEQ's concerns regarding immunotoxicity endpoints (e.g., decreased antibodies) are due to:

- Inconsistencies and lack of significance of results,

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[u] 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

- 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 PFOA and PFOS 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 PFOA 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 PFOA, there are no statistically significant odds ratios (ORs) for 5-year-old children with antibody titers in response to either diphtheria or tetanus vaccines, whereas 7-year-olds had statistically significant ORs for both (see eTable 4 of Grandjean et al. 2012). Similarly, for PFOS, the confidence intervals (95% CIs) of 3/4 ORs 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 key study cohort is for no statistically significant associations for PFOS with less-than-protective serum antibody concentrations in children (see eTable 4 of Grandjean et al. 2012).[v] 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 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*."[w] 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.

[v] The confidence interval (CI) for the one statistically significant OR of 1.60 (age 5, diphtheria) is (1.10, 2.34) (eTable 4 of Grandjean et al. 2012).

[w] 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.

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. An immediate problem with the study was the finding that the antibody titers increased from age 7 to 13 in almost half of the cohort (270 out of 587 children), when the titers should have decreased over that time. Sixty-eight children in that group likely received boosters, but that left 202 children with unexplained increases in titers. With that backdrop of uncertainty, the study authors looked at associations with antibody titers and concentrations of 5 PFAS (including PFOA and PFOS). However, the results are inconsistent depending on the cohort subgroup (total, without boosters, or only in children with titer decreases), the year of PFAS concentration collection (at 7 or 13 years old), and on the vaccine type. Most notably, while there were general trends of *decreasing diphtheria antibody titers* with increasing PFAS concentrations (although rarely were the associations statistically significant), there were general trends of *increasing tetanus antibody titers* with increasing PFAS concentrations (although rarely were the associations statistically significant). To conclude from this study that PFOA concentrations have significant adverse effects on antibody titers requires cherry-picking specific results and ignoring others that do not support the conclusion. For example, there was a statistically significant negative effect of PFOA concentrations measured at 13 years old on the change in anti-diphtheria titers in the cohort with no emergency room visits (a stand-in for children who likely had boosters), but not in the full cohort, or in the group of children who showed overall decreases in antibody titers. Additionally, there were no significant effects of PFOA on anti-tetanus titers, with overall positive trends in two of the cohort groupings. 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 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.[x] 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.[y] *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.

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), PFOS and PFOA were moderately correlated with each other (correlation coefficient of 0.50) and were correlated with other PFAS (e.g., coefficients of 0.53-0.57 for

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[x] 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.

[y] 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.

PFHxS, 0.35-0.39 for PFDA, and 0.48-0.54 for PFNA at age 5) that also had some statistically significant associations with antibody 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). Thus, for PFOS, PFOA, 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 PFOS or PFOA. 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 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 0.50 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; see Table 2 of the study). There were also low exposure contrasts in 7- and 13-year-olds, as the IQRs for PFOA and PFOS were ≤ 1.6 fold (Table 1 of Grandjean et al. 2017a).

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 Budtz-Jørgensen and Grandjean (2018) presents benchmark results for the serum concentrations from five PFAS chemicals measured prenatally with antibody concentrations at age 5 years (pre-booster) both unadjusted and adjusted for PFOS/PFOA co-exposures. For tetanus antibodies, unadjusted PFOA BMDs are very similar to the PFOA BMDs that include PFOS-adjustment, whereas adjusting the PFOS BMDs for PFOA results in all three tested models' being unable to fit the data (the generated BMDs = infinity). By contrast, for diphtheria, adjustment of PFOA models for PFOS, or PFOS models for PFOA, generate discrete BMDs, although the unadjusted vs. adjusted BMDs differed by as much as 4-fold for the PFOA BMDs. The inability of the models to generate BMD results for PFOS and tetanus antibodies when adjusting for PFOA demonstrate the potential for confounders (e.g., other PFAS) to significantly affect results when adjusting BMDs for only one co-exposure (PFOA). The bottom line is that results for PFOA and PFOS associations with these serum antibody endpoints (and BMDs) that adequately account for other relevant co-exposures (e.g., PFAS) are not available, and as mentioned above, PFOS and PFOA were not only correlated with each other but were also correlated with other PFAS (e.g., coefficients of 0.53-0.57 for PFHxS, 0.35-0.39 for PFDA, and 0.48-0.54 for PFNA at age 5) that had some statistically significant associations with antibody 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 PFOS and PFOA, 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).[z]

USEPA inappropriately uses PFOA risk estimates from models that do not control for confounding exposures and justifies this decision by arguing (without evidence) that controlling for confounding will cause confounding.

Classic confounding is likely for PFOS and PFOA epidemiologic results because PFAS exposures are correlated, they are chemically similar compounds, and some are potential

[z] 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).

immunotoxicants (e.g., Budtz-Jørgensen and Grandjean 2018). To justify their decision to use estimates that are not controlled for confounders, USEPA (2023) 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 (2023) 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. Such results include, but are not necessarily limited to, the following changes to PFOA-associated effects when controlling for PFOS: slope (β) values from linear regression being reduced for serum PFOA at age 5 predicting $\log_2$ tetanus antibodies measured at age 7 and for PFOA measured perinatally predicting diphtheria antibodies measured at age 5; serum PFOA measured perinatally becoming a nonsignificant predictor of tetanus antibodies measured at age 5; and serum PFOA measured at age 5 becoming a nonsignificant predictor of $\log_2$ diphtheria antibodies measured at age 7 (USEPA 2024a).

In contrast to the final assessment for PFOA and PFOS (USEPA 2023), USEPA's draft assessments for PFOA and PFOS (EPA 2021a,b) do not express any similar concerns about creating 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 PFOS/PFOA and the other PFAS examined are low-to-moderate (e.g., coefficients of 0.53-0.57 for PFHxS, 0.35-0.39 for PFDA, and 0.48-0.54 for PFNA at age 5 (Grandjean et al. 2012); Mukaka 2012). The results of Weisskopf et al. (2018) do not constitute reasonable doubt for PFOS, PFOA, 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 PFOA and PFOS exposure could be explained by confounding across*

the PFAS (see Section 3.3.4.1.1 of USEPA 2021a,b). Again, this issue calls into question the validity of the conclusions drawn from these studies, and the risk estimates derived from them.

Ground-Truthing Vaccine Findings Using Disease Rates

USEPA acknowledges that the evidence across studies for associations between PFAS and changes in disease rates (i.e., increased disease presumably due to diminished immunity) is inconsistent, resulting in low confidence in the evidence.

Regarding potential immunosuppression by PFOA or PFOS, 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. USEPA (2021a, p. 154) indicates that for associations of PFOA and increased incidences of disease, "inconsistency across studies reduces confidence in the evidence", and USEPA (2021b, p. 139) acknowledges for PFOS that "results were not consistent across studies", which similarly reduces confidence in the evidence. The inconsistent and low confidence evidence on infectious disease in humans is of obvious relevance to judgment concerning the adversity of the antibody concentration decreases associated with PFOS and PFOA 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 PFOS and PFOA associations with immunosuppressive effects (reduced antibody levels) resulting in demonstrable adverse effects (i.e., statistically increased incidences of diseases) attributable specifically to PFOS and PFOA exposures*.[aa] 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 1.7E-04 mg/L blood serum to 2.0E-04 mg/L blood serum for PFOA (from Table 21 of USEPA 2021a) and from 5.4E-04 mg/L blood serum to 7.2E-04 mg/L blood serum for PFOS (from Table

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

21 of USEPA 2021b).[bb] 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 6.7E-04 to 1.06E-03 mg/L for PFOA (Tables B-1 and B-2 of USEPA 2021a) and from 1.21E-03 to 3.57E-03 mg/L for PFOS (Tables B-2 and B-1 of USEPA 2021b). Data from NHANES show that geometric means (GMs) representative of the U.S. population are well above these blood serum levels.[cc] For example, 1999-2018 population GMs for PFOA range from 1.42 to 5.22 µg/L (1.42E-03 to 5.22E-03 mg/L) and the GM for children (2013-2014) is 1.96 µg/L (1.96E-03 mg/L), which are higher than the PODs and the BMDs. Similarly, for PFOS, the 1999-2018 population GMs range from 4.25 to 30.3 µg/L (4.25E-03 to 3.03E-02 mg/L) and the GM for children (2013-2014) is 3.9 µg/L (3.9E-03 mg/L), which are also higher than the PODs and BMDs. Despite the fact that PFOA and PFOS serum levels in the general U.S. population (and children specifically) exceed the levels at which EPA has concluded that antibody titers from vaccines are suppressed, 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.

[bb] The PODs are based on BMDLs (BMR of 5%), but the associated best estimates (BMDs) for PFOA are ≥ 3.9-fold higher than the BMDLs (Tables B-1 and B-2 of USEPA 2021a), and for PFOS are ≥ 2.2-fold higher than the BMDLs (Tables B-1 and B-2 of USEPA 2021b).

[cc] See NHANES Biomonitoring Data Tables in Appendix 4 of this document. Accessed from https://www.cdc.gov/exposurereport/data_tables.html. Budtz-Jørgensen & Grandjean (2018) also acknowledge that, "Our BMDL results, both before and after adjustment are generally below current exposure levels…"

> 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).[dd] *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 (2021a,b) human BMDs, 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 PFOA and/or PFOS (or any other serum PFAS) is suppressing tetanus and diphtheria vaccine responses and leaving people (adults or children) vulnerable to infection from these diseases.[ee]

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 (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:

[dd] 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

[ee] 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).

- the small number of studies and participants, and mostly cross-sectional design of studies such that *conclusions around causality should be drawn with caution*.
- 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.

Epidemiology Studies of Effects on Cholesterol

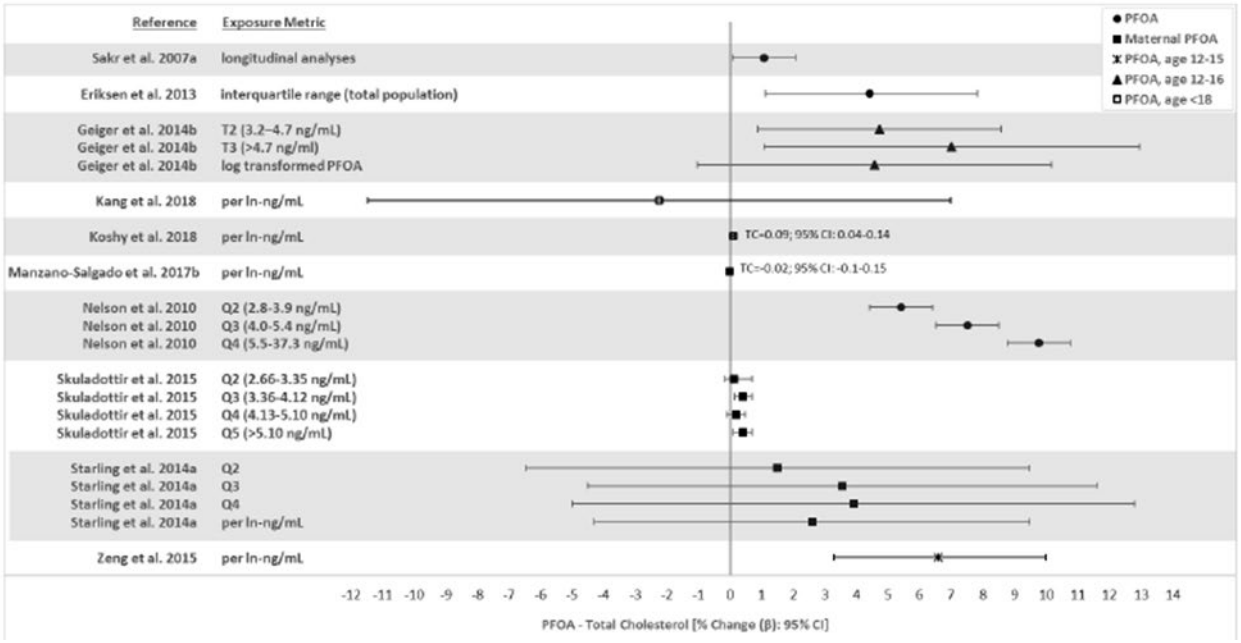
The epidemiology studies used to demonstrate effects of PFOA and PFOS on serum cholesterol report inconsistent results and have inadequate control for confounding.

As recently as October 2024 (Australian NHMRC 2024), the Australian Government has reaffirmed the position that the epidemiology literature is inadequate for use as the basis of

deriving toxicity factors for PFAS.[ff] Similarly, ATSDR (2021) indicates that while there are over 400 epidemiological studies, some of which provide evidence suggesting associations between PFAS exposure and health outcomes (such as increases in serum lipids, liver damage, thyroid disease, immune effects, reproductive toxicity, and developmental toxicity), the findings were not consistent across studies. Interpretation of the human data is limited by such issues as (not an exhaustive list): the reliance on cross-sectional studies that do not establish causality, unknown adversity of the observed effects, the lack of established cause-and-effect relationships for any effect, and the problem of PFAS co-exposures (pp. 749 and 751 of ATSDR 2021). This determination applies to both serum cholesterol results and the birth weight outcome discussed below.

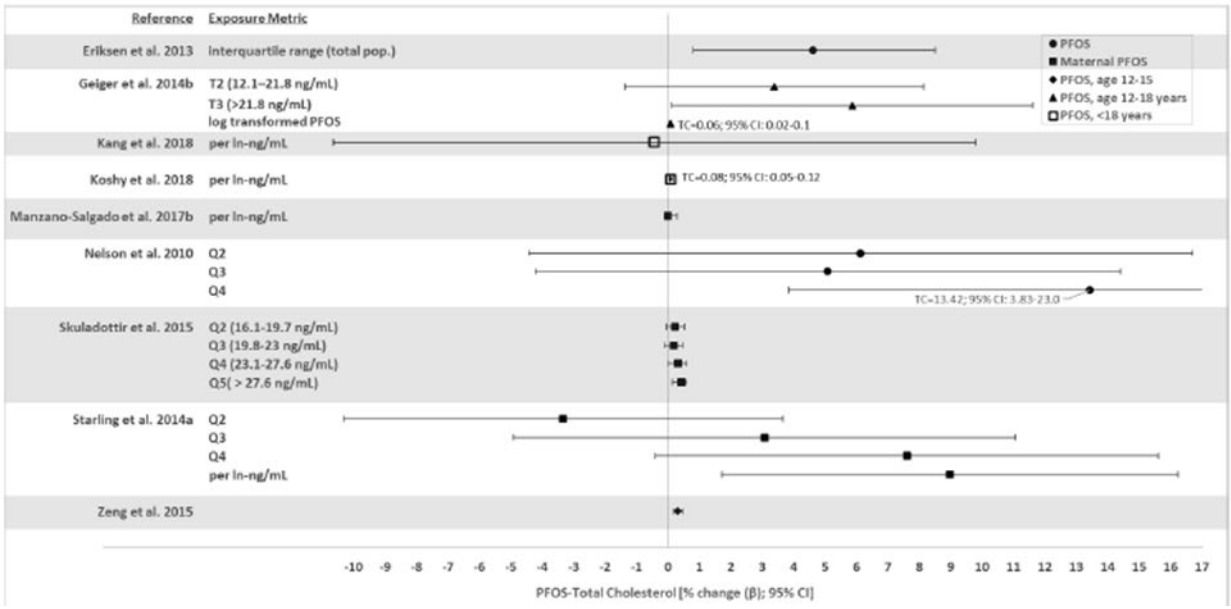
In regard to increased serum total cholesterol, Figures 2-11 and 2-15 from ATSDR (2021), reproduced below, show equivocal epidemiological WOE for PFOA- and PFOS-induced increased serum total cholesterol, with few studies reporting statistically significant results.

Figure 2-11. Serum Total Cholesterol Levels Relative to Serum PFOA Levels
(Presented as percent change in cholesterol levels)



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

Figure 2-15. Serum Total Cholesterol Levels Relative to Serum PFOS Levels
(Presented as percent change in cholesterol levels)



Moreover, because higher concentrations of serum low density lipoprotein (LDL) cholesterol are more routinely recognized as adverse, an examination of the odd ratios (ORs) in Figures 2-13 and 2-17 from ATSDR (2021), reproduced below, shows little evidence to support the epidemiological WOE for PFOA- and PFOS-induced increased serum LDL cholesterol. There is even weaker evidence from studies that investigated the relationship between PFOA or PFOS with abnormal LDL cholesterol levels (Figures 2-14 and 2-18, reproduced below). Many of the associations had very wide confidence intervals (demonstrating little confidence in the estimates) and included an estimate of zero effect.

Figure 2-13. Serum LDL Cholesterol Levels Relative to Serum PFOA Levels
(Presented as percent change in LDL cholesterol levels)

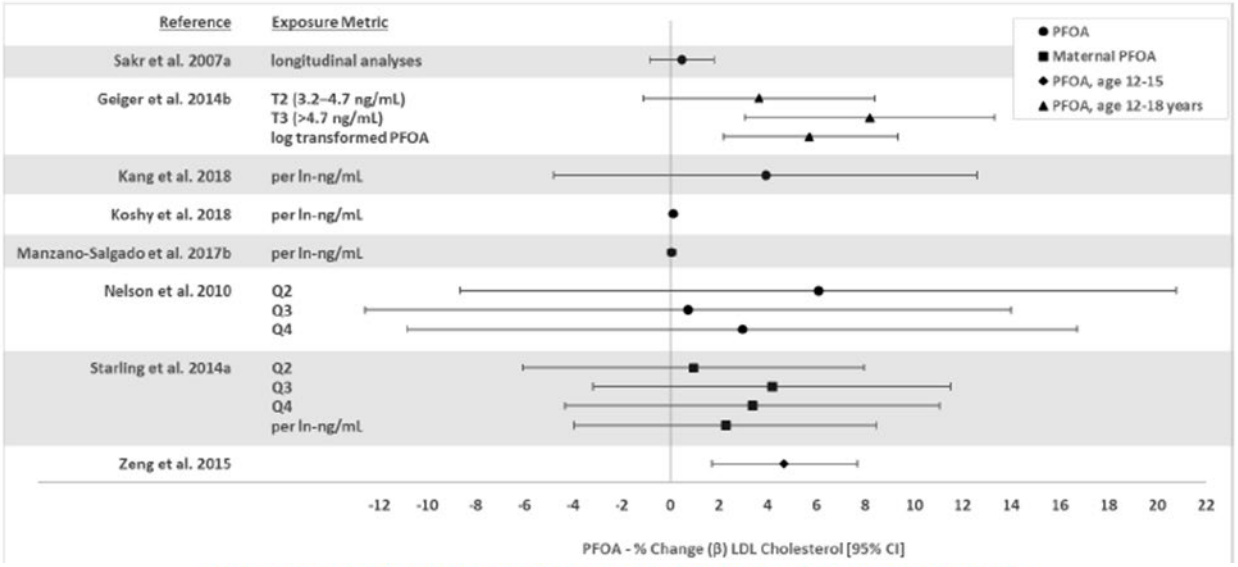


Figure 2-17. Serum LDL Cholesterol Levels Relative to Serum PFOS Levels
(Presented as percent change in LDL cholesterol levels)

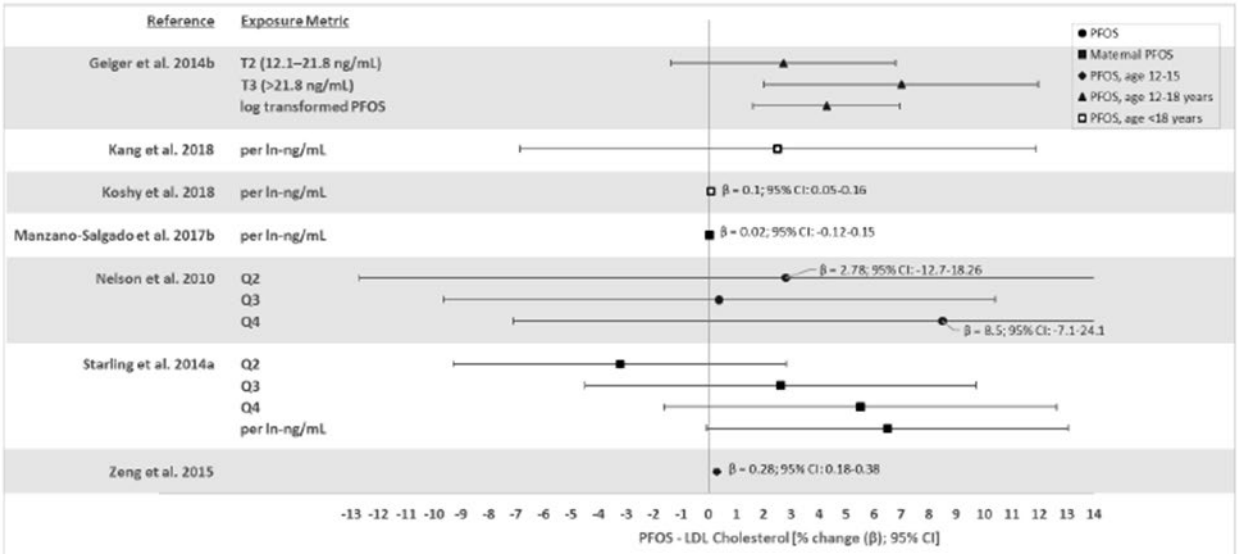


Figure 2-14. Risk of Abnormal LDL Cholesterol Levels Relative to PFOA Levels (Presented as Adjusted Ratios)

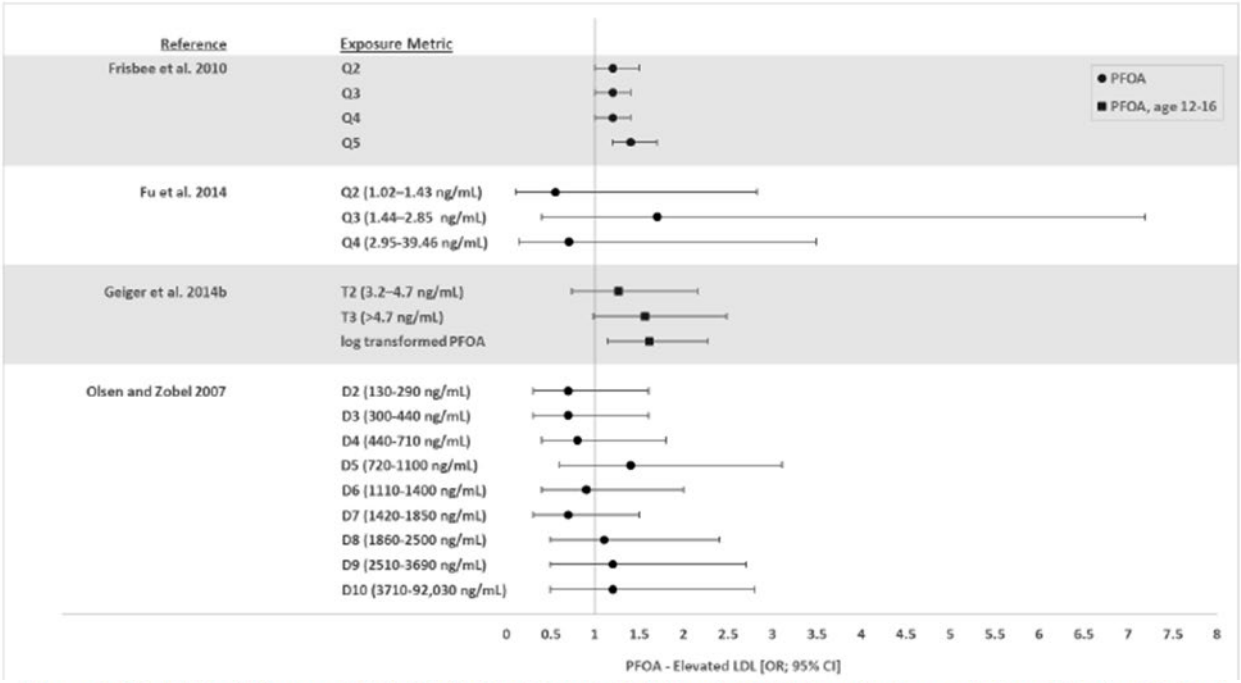
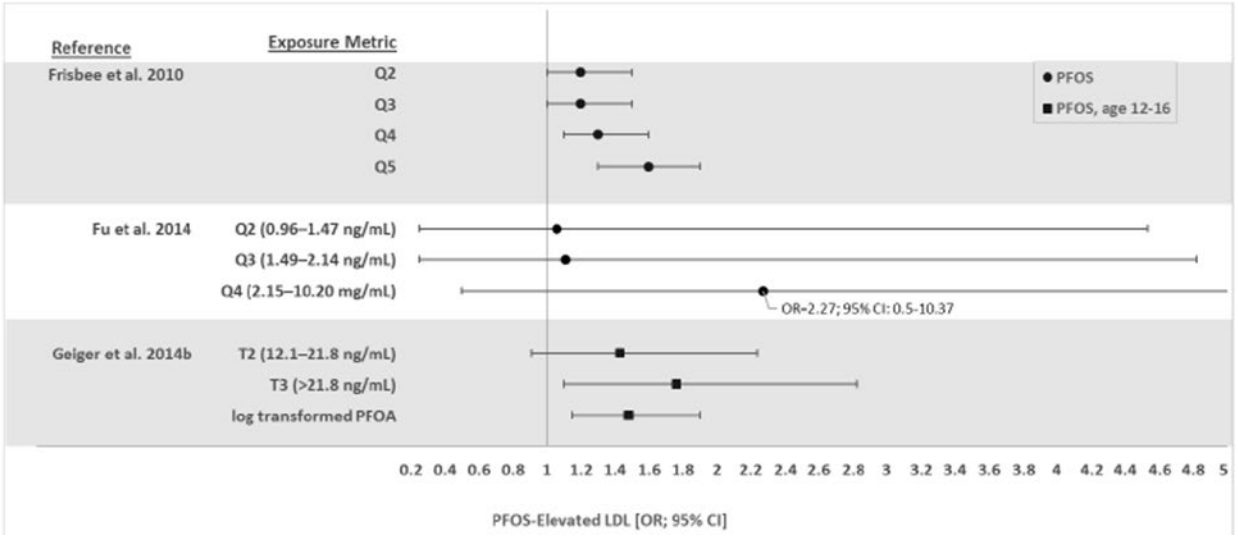


Figure 2-18. Risk of Abnormal LDL Cholesterol Levels Relative to PFOS Levels (Presented as Adjusted Ratios)



The Australian government recently reviewed Dong et al. (2019), the study underlying the increased serum total cholesterol association that EPA used as the partial basis for the PFOA and PFOS RfDs, to evaluate the scientific reliability of its findings and data (SLR 2024d). Their

review concluded that the data on dose-response from the Dong et al. (2019) study are not sufficiently reliable for use as a key study for derivation of a toxicity factor (e.g., RfD).[gg]

Epidemiology Studies of Birth Weight Effects

The epidemiology studies used to demonstrate effects of PFOA and PFOS on reduced birth weight report inconsistent results and have inadequate control for confounding.

EPA also uses low birth weight as a co-critical effect, which is an effect routinely recognized as adverse when there is evidence to support it. Figures 2-35 and 2-36 from ATSDR (2021), reproduced below, show that results from epidemiology studies investigating associations between PFOA and decreased birth weight or small for gestational age are rarely statistically significant and may indicate either positive or negative associations between PFOA and these endpoints. Therefore, the epidemiological WOE for PFOA-induced low birth weight is very poor.

[gg] As examples: limitations of the study include that it is cross-sectional and therefore cannot be used to attribute causality, only an association; that the study authors acknowledge that the study cannot determine whether exposure to PFAS elevates cholesterol levels or if high cholesterol levels simply facilitate PFAS storage in the blood (reverse causation), or whether joint factors simultaneously affect both PFAS and cholesterol; that other potential confounders (e.g., diet, albumin, etc.) may also impact cholesterol and were not adjusted for in the Dong et al. (2019) study; and that the study authors further acknowledge that the clinical significance of the elevations in cholesterol (i.e., adversity) was not investigated.

Figure 2-35. Risk of Low Birth Weight Infant Relative to PFOA Levels (Presented as Adjusted Odds Ratios)

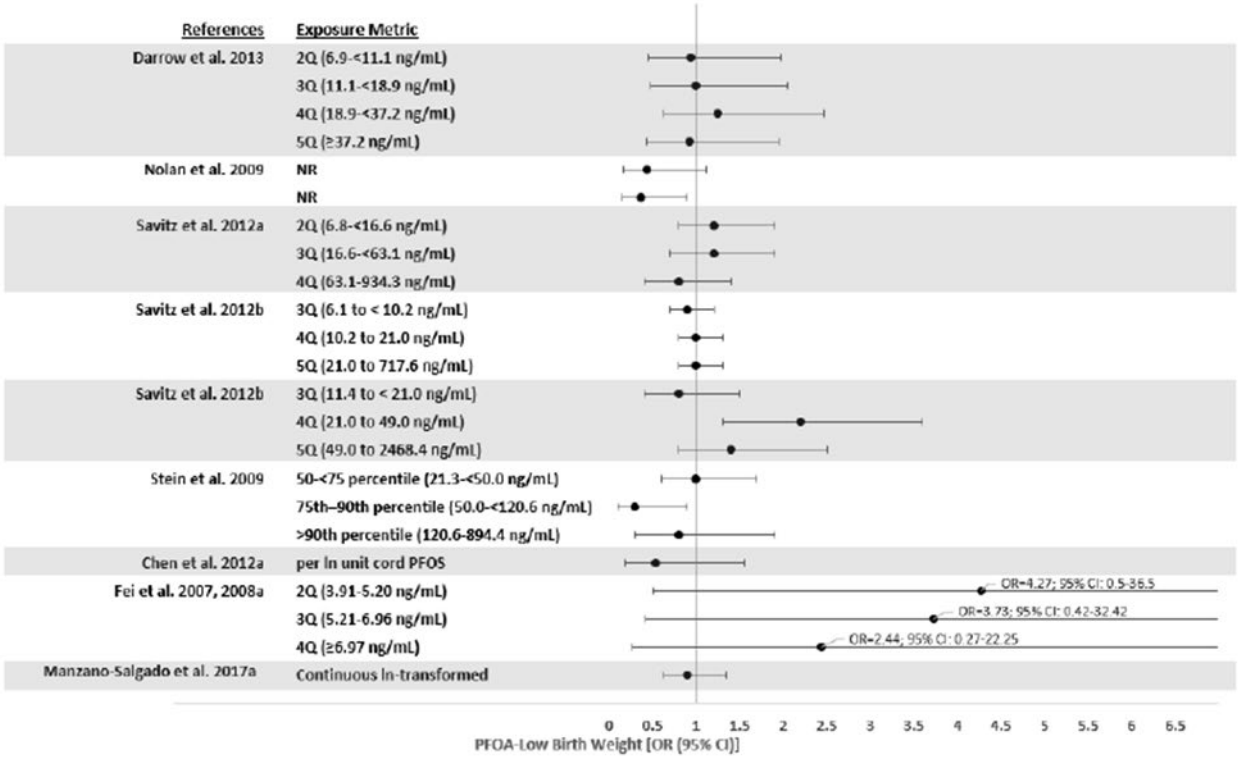
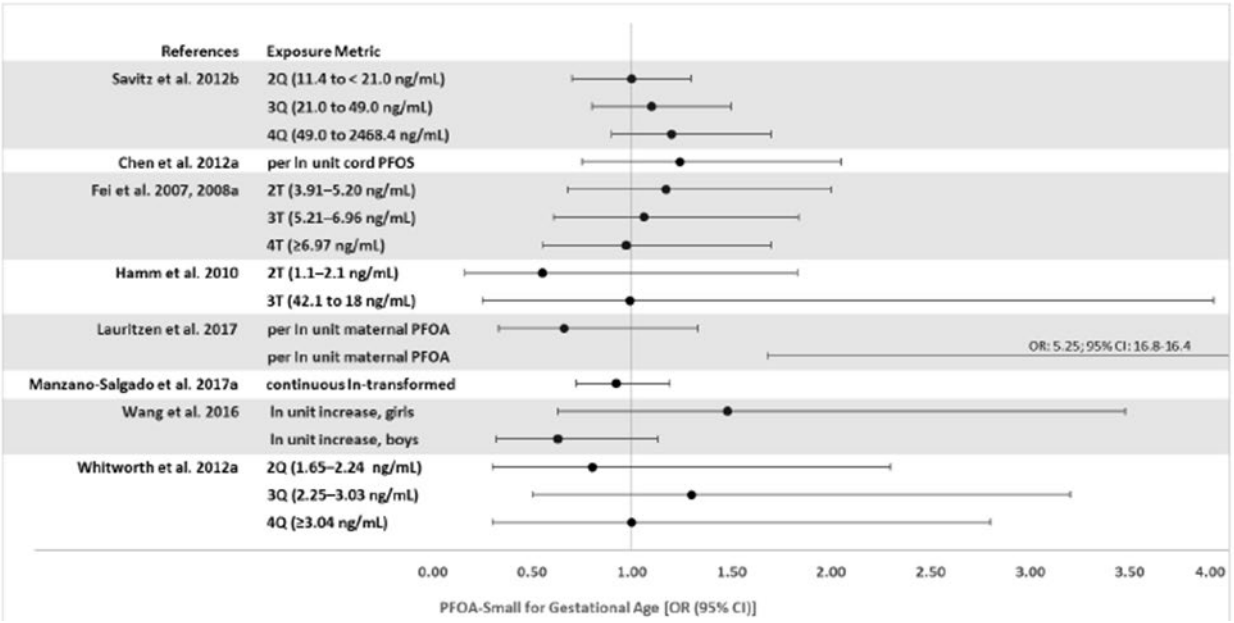
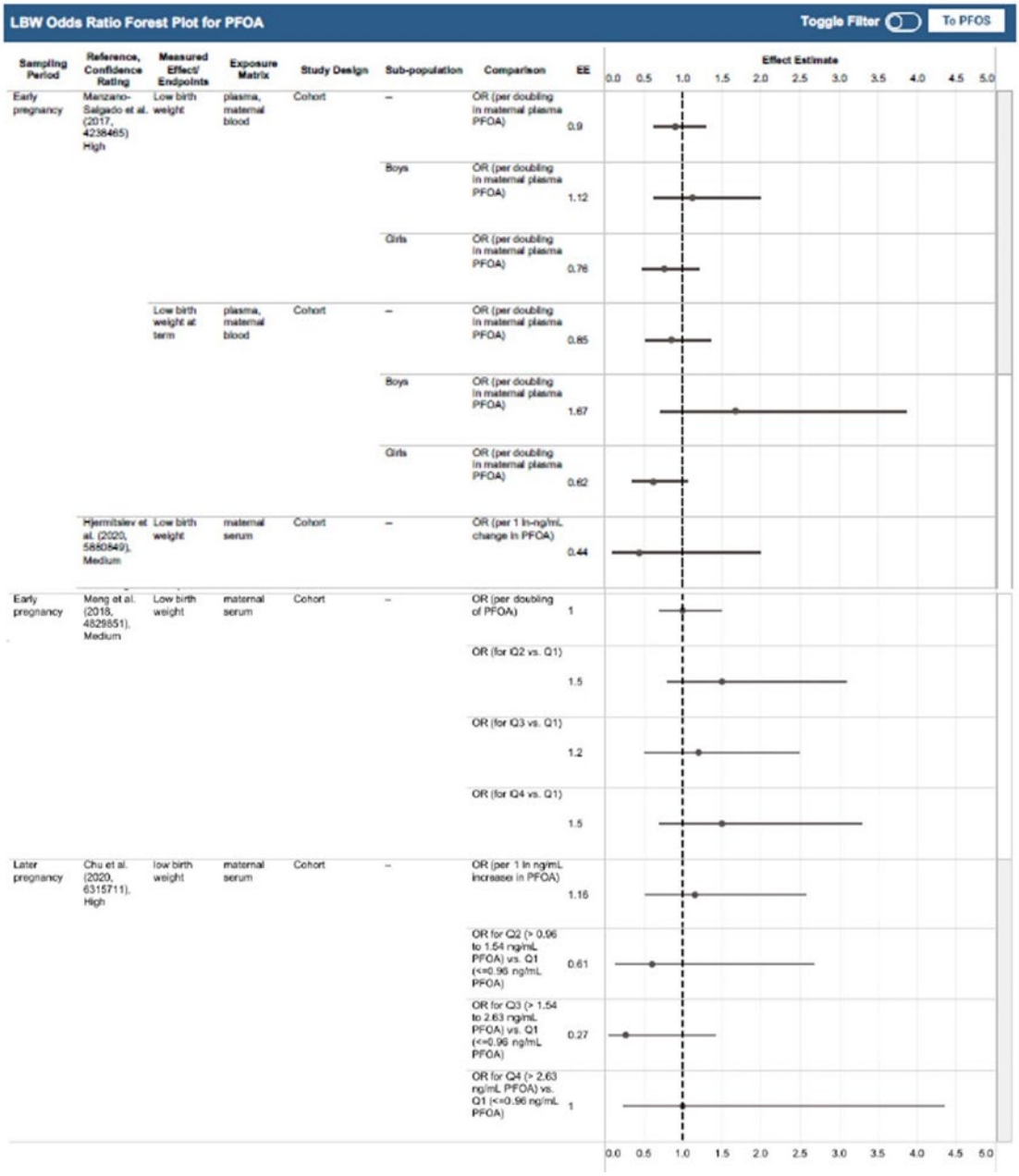


Figure 2-36. Risk of Small for Gestational Age Infant Relative to PFOA Levels (Presented as Adjusted Odds Ratios)



Similarly, the USEPA (2024a) HAWC data visualization odds ratio forest plot for PFOA-induced low birth weight (reproduced below)[hh] shows that results from epidemiology studies of PFOA-associated low birth weight are not statistically significant and have both positive and negative associations.

[hh] Available at: https://hawc.epa.gov/summary/visual/assessment/100500248/LBW-Odds-Ratio-Forest-Plot-for-PFOA/



The Australian government recently reviewed the study underlying the decreased birth weight partial basis for the PFOA and PFOS RfDs (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).[ii]

Comparison of TCEQ Conclusions to Other Agencies' Conclusions

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

TCEQ concurs with ATSDR (2021), which found that the epidemiology literature are 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*."

[ii] As examples: as a common limitation of epidemiological studies, it was not possible to control for all possible confounders; 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); while an effect on birth weight is qualitatively concordant with effects observed in experimental animal studies in rodent pups, it is difficult to reconcile the PFOS and PFOA serum concentrations that caused reductions in pup body weight gain in rodent studies (e.g., PFOS: maternal and F_1 males mean, respectively, of approximately 18,900 or 45,400 ng/mL, with no effects at approximately 5,280 or 10,500 ng/mL in Luebker et al. 2005; PFOA: maternal mean of 40,500 ng/mL, with no effects at 21,900 ng/mL in Lau et al. 2006), which are more than 10,000-times higher than the human serum PFOS and PFOA concentrations in the Wikström et al. (2020) study that are associated with decreased birth weight in infants (i.e. PFOS median of 5.38 ng/mL, PFOA median of 1.61 ng/mL); the interquartile range of PFOS/PFOA serum concentrations in the Wikström et al. (2020) study is very small in terms of absolute values (i.e., PFOS: 3.97-7.6, PFOA: 1.11-2.3 ng/mL), meaning that there is little difference in lower vs. higher PFOS/PFOA and calling into question the effects attributed at "higher" PFOS/PFOA levels; USEPA's BMDL values (7.7 ng/mL for PFOS, 2.2 ng/mL for PFOA; EPA 2024a,b) are similar to the 75th percentile of maternal serum PFOS/PFOA concentrations and all study children birth weights being within the normal range (3,290 - 3,998 g), making it difficult to reconcile whether such low serum PFOS and PFOA concentrations relative to the serum PFOS and PFOA concentrations observed in experimental animals are to be believed as exerting a true adverse effect. These considerations 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 PFOS and PFOA exposure.

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, and increased serum total cholesterol in adults) *is inadequate for quantitative risk assessment and use as the basis for deriving toxicity factors (e.g., RfDs) for PFAS, including PFOA and PFOS*. 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, and increased serum total cholesterol in adults) is inadequate for quantitative risk assessment and for use as the basis for deriving toxicity factors (e.g., RfDs) for PFOA and PFOS.

Appendix 4 NHANES Blood Serum Data for PFOA and PFOS

Serum Perfluorooctanoic acid (PFOA) (1999-2000, 2003-2010)

CAS Number 335-67-1

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	5.22 (4.72-5.78)	5.20 (4.80-5.90)	7.00 (6.30-7.80)	9.60 (8.20-11.2)	11.9 (11.0-13.5)	1432
Total population	03-04	3.95 (3.65-4.27)	4.10 (3.80-4.40)	5.80 (5.30-6.40)	7.80 (6.70-9.60)	9.80 (7.40-14.1)	2094
Total population	05-06	3.92 (3.48-4.42)	4.20 (3.80-4.50)	6.20 (5.40-7.20)	9.00 (7.40-11.2)	11.3 (8.80-14.5)	2120
Total population	07-08	4.12 (4.01-4.24)	4.30 (4.20-4.50)	5.90 (5.70-6.20)	7.90 (7.50-8.30)	9.60 (8.90-10.1)	2100
Total population	09-10	3.07 (2.81-3.36)	3.20 (2.90-3.50)	4.60 (4.10-5.10)	6.00 (5.30-7.20)	7.50 (6.20-9.70)	2233
Age 12-19 years	99-00	5.50 (5.00-6.05)	5.60 (4.80-6.20)	6.90 (6.20-7.90)	9.50 (7.70-11.1)	11.6 (10.0-12.5)	497
Age 12-19 years	03-04	3.89 (3.47-4.35)	4.00 (3.50-4.50)	5.40 (4.60-6.10)	7.00 (5.60-9.20)	8.60 (5.90-12.6)	640
Age 12-19 years	05-06	3.59 (3.26-3.96)	3.80 (3.30-4.20)	5.40 (4.60-5.90)	6.90 (6.30-7.90)	8.40 (7.30-10.1)	640
Age 12-19 years	07-08	3.91 (3.71-4.12)	4.00 (3.70-4.40)	5.00 (4.70-5.50)	6.10 (5.70-6.70)	7.30 (6.20-8.00)	357
Age 12-19 years	09-10	2.74 (2.46-3.05)	2.90 (2.60-3.10)	3.80 (3.30-4.20)	4.80 (4.10-5.30)	5.00 (4.40-7.20)	364
Age 20+ years	99-00	5.18 (4.66-5.75)	5.20 (4.70-5.80)	7.00 (6.30-7.80)	9.60 (8.20-11.3)	12.1 (10.6-14.4)	935
Age 20+ years	03-04	3.96 (3.67-4.27)	4.10 (3.90-4.40)	5.90 (5.40-6.50)	7.80 (6.80-9.60)	9.90 (7.60-14.2)	1454
Age 20+ years	05-06	3.97 (3.51-4.49)	4.20 (3.80-4.60)	6.40 (5.40-7.50)	9.30 (7.40-11.9)	11.6 (9.00-14.8)	1480
Age 20+ years	07-08	4.15 (4.02-4.30)	4.30 (4.20-4.60)	6.10 (5.80-6.50)	8.10 (7.70-8.70)	9.80 (9.00-10.4)	1743
Age 20+ years	09-10	3.12 (2.84-3.43)	3.30 (3.00-3.60)	4.70 (4.20-5.30)	6.40 (5.40-7.50)	7.70 (6.30-10.2)	1869
Males	99-00	5.75 (5.20-6.36)	6.00 (5.40-6.50)	7.80 (6.90-8.70)	10.6 (8.80-11.9)	12.3 (11.2-13.2)	684
Males	03-04	4.47 (4.07-4.91)	4.60 (4.30-5.00)	6.30 (5.70-7.20)	8.40 (6.80-12.5)	10.7 (7.40-17.5)	1053
Males	05-06	4.69 (4.23-5.20)	4.90 (4.40-5.40)	7.20 (6.10-8.00)	9.90 (8.00-12.2)	12.2 (9.60-15.2)	1048
Males	07-08	4.80 (4.55-5.06)	4.90 (4.60-5.20)	6.70 (6.30-7.10)	8.70 (8.10-9.30)	10.1 (9.50-11.1)	1059
Males	09-10	3.53 (3.22-3.87)	3.70 (3.40-4.00)	4.90 (4.50-5.40)	6.80 (5.40-8.00)	7.90 (6.40-10.2)	1075
Females	99-00	4.80 (4.29-5.37)	4.70 (4.40-5.10)	6.30 (5.60-7.10)	8.30 (7.40-10.0)	11.3 (9.20-14.4)	748
Females	03-04	3.50 (3.21-3.82)	3.60 (3.30-3.90)	5.20 (4.70-5.80)	7.10 (6.30-8.20)	8.60 (7.40-10.6)	1041
Females	05-06	3.31 (2.89-3.79)	3.50 (3.10-4.00)	5.20 (4.40-6.00)	7.90 (6.10-9.70)	10.1 (7.50-14.2)	1072
Females	07-08	3.55 (3.38-3.73)	3.70 (3.50-3.90)	5.20 (4.80-5.60)	7.00 (6.50-7.50)	8.30 (7.20-9.90)	1041
Females	09-10	2.69 (2.45-2.96)	2.70 (2.50-3.00)	4.10 (3.60-4.70)	5.60 (5.10-6.50)	6.90 (5.80-8.40)	1158
Mexican Americans	99-00	3.87 (3.55-4.23)	4.20 (3.80-4.60)	5.90 (5.20-6.40)	7.70 (6.30-8.20)	8.20 (7.80-9.20)	521
Mexican Americans	03-04	3.11 (2.84-3.40)	3.30 (3.10-3.70)	4.50 (4.20-5.20)	6.70 (5.70-7.30)	7.60 (6.70-10.5)	485
Mexican Americans	05-06	2.62 (2.33-2.95)	2.80 (2.50-3.30)	4.30 (3.80-4.70)	5.80 (5.30-6.70)	7.40 (5.90-8.10)	499
Mexican Americans	07-08	3.54 (3.35-3.75)	3.80 (3.50-4.00)	5.20 (4.90-5.60)	6.60 (6.20-7.10)	7.60 (6.80-9.00)	391
Mexican Americans	09-10	2.26 (2.00-2.54)	2.40 (2.10-2.60)	3.60 (3.10-3.80)	4.60 (4.00-5.30)	5.40 (4.50-6.60)	461
Non-Hispanic Blacks	99-00	4.85 (4.20-5.59)	4.90 (4.10-5.90)	6.40 (5.90-7.50)	9.00 (7.30-11.5)	11.1 (9.20-13.5)	269
Non-Hispanic Blacks	03-04	3.37 (2.99-3.79)	3.70 (3.20-4.20)	5.20 (4.40-6.30)	7.70 (5.30-11.6)	9.60 (6.50-13.9)	538
Non-Hispanic Blacks	05-06	3.27 (2.61-4.08)	3.70 (3.00-4.20)	5.50 (4.40-6.80)	8.10 (6.00-11.3)	10.4 (7.80-12.3)	544
Non-Hispanic Blacks	07-08	3.86 (3.57-4.16)	4.00 (3.50-4.30)	5.90 (5.20-6.50)	7.80 (7.10-8.70)	9.20 (8.50-10.1)	419
Non-Hispanic Blacks	09-10	2.74 (2.47-3.04)	2.80 (2.60-3.00)	4.00 (3.70-4.40)	5.50 (5.00-6.20)	6.70 (5.60-9.40)	391
Non-Hispanic Whites	99-00	5.62 (5.04-6.27)	5.60 (4.90-6.20)	7.30 (6.50-8.30)	10.5 (8.30-12.9)	13.1 (11.0-15.6)	491
Non-Hispanic Whites	03-04	4.18 (3.85-4.53)	4.30 (3.90-4.70)	6.00 (5.50-6.70)	7.90 (7.20-9.20)	9.90 (7.60-13.3)	962
Non-Hispanic Whites	05-06	4.27 (3.80-4.81)	4.40 (4.00-5.00)	6.60 (5.60-7.80)	9.60 (7.40-12.2)	11.6 (8.80-14.8)	935
Non-Hispanic Whites	07-08	4.38 (4.20-4.56)	4.60 (4.30-4.70)	6.10 (5.80-6.60)	8.20 (7.80-8.80)	9.90 (9.30-10.6)	931
Non-Hispanic Whites	09-10	3.36 (3.06-3.69)	3.50 (3.20-3.90)	4.80 (4.40-5.40)	6.60 (5.40-7.80)	7.80 (6.20-10.5)	1031

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

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

Serum Perfluorooctanoic acid (PFOA) (2011 - 2018)

Sum of linear and branched PFOA isomers

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	2.08 (1.95-2.22)	2.08 (1.96-2.26)	3.03 (2.76-3.27)	4.35 (3.82-4.85)	5.68 (5.02-6.49)	1904
Total population	13-14	1.94 (1.76-2.15)	2.07 (1.87-2.20)	3.07 (2.67-3.37)	4.27 (3.57-5.17)	5.57 (4.60-6.27)	1954
Total population	15-16	1.56 (1.47-1.66)	1.57 (1.47-1.77)	2.47 (2.27-2.57)	3.37 (3.07-3.57)	4.17 (3.87-4.67)	1993
Total population	17-18	1.42 (1.33-1.52)	1.47 (1.37-1.57)	2.07 (1.97-2.30)	2.97 (2.77-3.37)	3.77 (3.17-5.07)	1929
Age 12-19 years	11-12	1.80 (1.71-1.91)	1.74 (1.67-1.89)	2.41 (2.17-2.62)	2.93 (2.68-3.19)	3.59 (2.93-4.25)	344
Age 12-19 years	13-14	1.67 (1.51-1.86)	1.67 (1.40-1.97)	2.20 (2.00-2.57)	2.87 (2.57-3.40)	3.47 (2.80-3.77)	348
Age 12-19 years	15-16	1.25 (1.14-1.37)	1.27 (1.17-1.47)	1.67 (1.47-1.87)	2.07 (1.77-2.57)	2.47 (2.07-2.97)	353
Age 12-19 years	17-18	1.18 (1.06-1.31)	1.17 (1.00-1.37)	1.67 (1.37-1.97)	2.07 (1.77-2.37)	2.37 (2.00-2.97)	313
Age 20+ years	11-12	2.12 (1.98-2.28)	2.16 (2.01-2.33)	3.15 (2.90-3.36)	4.64 (3.93-5.25)	5.94 (5.34-7.45)	1560
Age 20+ years	13-14	1.98 (1.79-2.20)	2.07 (1.97-2.27)	3.17 (2.77-3.47)	4.50 (3.70-5.37)	5.67 (4.70-6.40)	1606
Age 20+ years	15-16	1.60 (1.51-1.71)	1.67 (1.57-1.87)	2.47 (2.37-2.67)	3.47 (3.17-3.67)	4.27 (4.07-4.97)	1640
Age 20+ years	17-18	1.45 (1.35-1.56)	1.47 (1.37-1.57)	2.17 (1.97-2.37)	3.17 (2.77-3.57)	3.87 (3.27-5.17)	1616
Males	11-12	2.37 (2.22-2.53)	2.38 (2.26-2.56)	3.25 (3.00-3.56)	4.61 (4.11-5.02)	5.62 (4.85-6.20)	966
Males	13-14	2.28 (2.08-2.50)	2.30 (2.10-2.57)	3.27 (2.87-3.60)	4.67 (3.77-5.60)	5.67 (4.67-6.27)	931
Males	15-16	1.80 (1.66-1.94)	1.87 (1.67-2.07)	2.57 (2.40-2.67)	3.37 (3.07-3.67)	4.07 (3.67-4.87)	964
Males	17-18	1.61 (1.50-1.73)	1.57 (1.47-1.77)	2.17 (2.07-2.37)	3.17 (2.77-3.50)	3.77 (3.27-5.17)	952
Females	11-12	1.84 (1.68-2.01)	1.78 (1.62-1.98)	2.65 (2.34-3.14)	3.91 (3.36-4.99)	5.68 (4.33-8.45)	938
Females	13-14	1.67 (1.48-1.88)	1.67 (1.47-1.90)	2.67 (2.30-3.07)	3.77 (3.37-4.80)	5.07 (4.17-6.47)	1023
Females	15-16	1.36 (1.29-1.45)	1.37 (1.27-1.47)	2.17 (1.97-2.47)	3.37 (2.87-3.67)	4.17 (3.67-4.97)	1029
Females	17-18	1.26 (1.17-1.36)	1.27 (1.17-1.37)	1.97 (1.77-2.20)	2.97 (2.57-3.37)	3.77 (2.97-5.07)	977
Mexican Americans	11-12	1.66 (1.37-2.02)	1.71 (1.32-2.23)	2.43 (1.98-2.98)	3.38 (2.43-4.48)	4.08 (2.98-6.15)	211
Mexican Americans	13-14	1.37 (1.25-1.50)	1.37 (1.27-1.47)	1.97 (1.80-2.20)	2.70 (2.40-3.17)	3.17 (2.60-3.97)	297
Mexican Americans	15-16	1.14 (1.01-1.28)	1.17 (1.07-1.27)	1.67 (1.47-1.87)	2.47 (1.87-2.97)	2.77 (2.20-4.67)	370
Mexican Americans	17-18	1.11 (.967-1.27)	1.17 (.870-1.37)	1.57 (1.37-1.87)	2.17 (1.87-2.37)	2.80 (2.37-4.20)	297
Non-Hispanic Blacks	11-12	1.80 (1.71-1.90)	1.94 (1.76-2.09)	2.82 (2.65-2.95)	3.94 (3.51-4.40)	5.11 (4.40-5.79)	485
Non-Hispanic Blacks	13-14	1.50 (1.31-1.73)	1.67 (1.27-1.97)	2.57 (2.07-2.97)	3.60 (3.07-4.47)	4.60 (3.30-5.90)	389
Non-Hispanic Blacks	15-16	1.36 (1.21-1.53)	1.37 (1.27-1.57)	2.17 (1.97-2.57)	3.37 (2.77-3.77)	4.07 (3.57-5.27)	439
Non-Hispanic Blacks	17-18	1.18 (1.08-1.30)	1.27 (1.07-1.47)	1.77 (1.67-1.97)	2.70 (2.27-2.97)	3.37 (2.77-4.27)	430
Non-Hispanic Whites	11-12	2.25 (2.05-2.47)	2.25 (1.98-2.48)	3.21 (2.90-3.50)	4.68 (3.95-5.35)	6.20 (5.34-7.74)	666
Non-Hispanic Whites	13-14	2.20 (1.91-2.53)	2.27 (1.97-2.67)	3.37 (2.77-3.77)	4.77 (3.77-5.70)	5.77 (4.80-6.80)	805
Non-Hispanic Whites	15-16	1.69 (1.57-1.82)	1.77 (1.57-1.97)	2.57 (2.47-2.67)	3.47 (3.17-3.67)	4.47 (3.87-5.17)	619
Non-Hispanic Whites	17-18	1.54 (1.41-1.69)	1.57 (1.37-1.77)	2.27 (2.07-2.47)	3.17 (2.77-3.67)	3.77 (3.07-5.47)	667
All Hispanics	11-12	1.70 (1.48-1.95)	1.79 (1.59-1.95)	2.46 (2.15-2.91)	3.60 (2.95-4.48)	4.70 (3.87-5.94)	406
All Hispanics	13-14	1.46 (1.33-1.61)	1.47 (1.37-1.67)	2.10 (1.90-2.47)	3.07 (2.60-3.17)	3.57 (3.17-3.97)	488
All Hispanics	15-16	1.25 (1.14-1.36)	1.27 (1.17-1.47)	1.87 (1.67-2.20)	2.67 (2.37-3.07)	3.17 (2.77-4.17)	629
All Hispanics	17-18	1.19 (1.07-1.32)	1.27 (1.07-1.37)	1.67 (1.47-1.87)	2.37 (2.07-2.67)	2.97 (2.50-4.37)	473
Asians	11-12	2.08 (1.83-2.36)	2.21 (2.04-2.27)	2.92 (2.55-3.45)	4.66 (3.42-5.79)	5.79 (4.93-8.91)	291
Asians	13-14	2.03 (1.77-2.33)	1.97 (1.70-2.37)	3.07 (2.57-4.07)	4.77 (4.17-5.77)	5.90 (5.00-6.40)	203
Asians	15-16	1.66 (1.42-1.94)	1.77 (1.37-2.07)	2.37 (2.17-2.87)	3.77 (2.97-4.47)	4.77 (3.87-7.57)	220
Asians	17-18	1.65 (1.38-1.97)	1.50 (1.37-1.77)	2.67 (2.07-3.40)	4.67 (2.57-9.87)	6.77 (3.40-17.0)	257

Limit of detection (LOD, see Data Analysis section) for Survey year 11-12 is 0.1.

‡See Calculation of PFOS and PFOA as the Sum of Isomers for additional information about Survey years 2013-2014, 2015-2016, and 2017-2018.

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

Serum estimated PFOA (total) (Special Sample of Serum PFAS in Children, 2013-2014)

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	1.96 (1.76-2.17)	1.95 (1.67-2.23)	2.70 (2.42-3.10)	3.69 (3.27-4.14)	4.23 (3.84-5.47)	525
Age 3-5 years	13-14	2.04 (1.77-2.36)	1.82 (1.64-2.40)	3.23 (2.70-3.52)	4.22 (2.88-5.86)	5.86 (3.28-7.02)	149
Age 6-11 years	13-14	1.92 (1.73-2.12)	1.97 (1.69-2.18)	2.56 (2.25-2.91)	3.38 (2.97-3.84)	3.99 (3.53-4.14)	376
Males	13-14	1.94 (1.74-2.17)	1.88 (1.62-2.19)	2.71 (2.19-3.38)	3.72 (3.28-4.14)	4.14 (3.46-5.86)	284
Females	13-14	1.97 (1.74-2.24)	2.00 (1.71-2.27)	2.68 (2.35-2.97)	3.60 (2.88-4.22)	4.24 (3.17-7.02)	241
All Hispanics	13-14	1.73 (1.56-1.92)	1.69 (1.55-1.94)	2.32 (2.05-2.67)	2.95 (2.52-3.41)	3.41 (2.83-4.01)	186
Other	13-14	2.04 (1.80-2.30)	2.04 (1.71-2.42)	2.87 (2.51-3.28)	3.99 (3.28-5.15)	5.15 (3.72-5.86)	339

* See Calculation of PFOS and PFOA as the Sum of Isomers for additional information about Survey years 2013-2014.

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

Serum Perfluorooctane sulfonic acid (PFOS) (1999-2000, 2003-2010)

CAS Number 1763-23-1

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	30.3 (27.1-33.9)	30.2 (27.8-33.9)	43.8 (37.5-47.6)	56.8 (50.2-70.0)	75.7 (58.9-97.5)	1432
Total population	03-04	20.7 (19.2-22.3)	21.2 (19.8-22.4)	30.0 (27.5-33.0)	41.3 (35.6-50.0)	54.6 (44.0-66.5)	2094
Total population	05-06	17.1 (16.0-18.2)	17.5 (16.8-18.6)	27.2 (24.9-29.6)	39.4 (34.9-43.1)	47.5 (42.7-56.8)	2120
Total population	07-08	13.2 (12.2-14.2)	13.6 (12.8-14.7)	21.0 (18.9-23.3)	32.6 (29.4-36.3)	40.5 (35.4-47.4)	2100
Total population	09-10	9.32 (8.13-10.7)	9.70 (8.50-10.8)	14.8 (12.9-17.3)	23.7 (18.3-30.2)	32.0 (22.6-48.5)	2233
Age 12-19 years	99-00	29.0 (26.1-32.3)	29.5 (26.9-34.2)	38.1 (35.9-43.8)	52.7 (45.3-56.6)	57.6 (52.7-70.0)	497
Age 12-19 years	03-04	19.3 (17.5-21.4)	19.9 (17.8-22.0)	27.1 (23.7-30.2)	36.5 (28.6-45.6)	42.6 (35.1-52.1)	640
Age 12-19 years	05-06	15.0 (14.3-15.7)	14.9 (13.6-16.6)	22.7 (19.7-24.9)	30.6 (27.8-34.1)	38.5 (33.0-44.6)	640
Age 12-19 years	07-08	11.3 (10.3-12.3)	11.3 (10.3-13.0)	15.9 (15.1-17.7)	21.7 (17.7-28.2)	28.0 (22.0-32.2)	357
Age 12-19 years	09-10	6.84 (5.81-8.06)	6.90 (6.00-8.40)	10.7 (8.90-12.5)	14.4 (12.4-18.1)	18.1 (13.5-26.0)	364
Age 20+ years	99-00	30.6 (27.1-34.4)	30.3 (27.9-33.9)	44.7 (38.1-48.4)	57.5 (50.4-75.5)	78.0 (60.4-108)	935
Age 20+ years	03-04	20.9 (19.3-22.5)	21.4 (19.8-22.8)	30.4 (28.1-33.0)	42.7 (35.7-53.3)	57.8 (45.7-69.4)	1454
Age 20+ years	05-06	17.4 (16.2-18.7)	18.0 (17.1-19.4)	27.8 (25.3-30.8)	40.2 (35.6-44.5)	49.6 (42.8-60.7)	1480
Age 20+ years	07-08	13.5 (12.4-14.6)	14.0 (13.0-15.5)	21.7 (19.5-24.6)	33.9 (29.9-39.0)	42.8 (37.3-50.3)	1743
Age 20+ years	09-10	9.72 (8.45-11.2)	10.1 (8.90-11.2)	15.7 (13.4-18.4)	25.3 (19.3-32.9)	34.1 (23.4-52.7)	1869
Males	99-00	33.5 (29.7-37.7)	35.0 (31.5-38.1)	46.4 (41.0-51.9)	58.4 (50.2-76.5)	75.3 (56.9-108)	684
Males	03-04	23.2 (21.1-25.6)	23.9 (22.4-25.5)	32.2 (28.8-35.9)	45.3 (35.5-62.7)	62.7 (43.8-81.8)	1053
Males	05-06	20.5 (19.4-21.8)	21.3 (20.0-22.5)	31.4 (27.9-33.7)	43.3 (38.7-49.7)	54.3 (43.5-80.7)	1048
Males	07-08	16.3 (15.0-17.7)	17.0 (15.7-17.8)	23.9 (21.6-26.9)	36.4 (33.5-41.1)	45.3 (40.4-53.1)	1059
Males	09-10	11.5 (9.93-13.3)	11.8 (10.6-12.9)	16.8 (14.3-20.4)	25.7 (19.4-39.7)	37.4 (22.5-72.3)	1075
Females	99-00	27.8 (24.4-31.7)	27.8 (24.1-30.2)	38.7 (32.3-46.3)	55.4 (46.5-72.6)	75.7 (55.5-98.4)	748
Females	03-04	18.4 (17.0-20.0)	18.2 (16.9-19.8)	27.4 (23.8-30.2)	39.8 (34.4-42.6)	46.6 (42.3-61.5)	1041
Females	05-06	14.4 (13.3-15.4)	14.6 (13.5-15.9)	23.3 (21.1-25.3)	34.2 (30.6-37.7)	42.8 (38.0-46.5)	1072
Females	07-08	10.7 (9.70-11.7)	10.7 (9.80-11.7)	17.2 (15.4-19.1)	28.7 (21.7-32.5)	33.6 (29.9-41.6)	1041
Females	09-10	7.65 (6.73-8.71)	7.80 (6.70-9.00)	12.0 (10.8-14.4)	21.1 (16.4-26.9)	28.8 (22.3-34.1)	1158
Mexican Americans	99-00	22.7 (19.6-26.3)	24.1 (20.4-27.8)	33.1 (27.8-39.7)	43.5 (36.1-57.5)	56.6 (40.5-81.5)	521
Mexican Americans	03-04	14.7 (13.0-16.6)	15.9 (13.4-17.9)	21.2 (18.7-23.5)	28.1 (24.1-35.0)	35.5 (28.9-38.5)	485
Mexican Americans	05-06	11.2 (10.3-12.2)	11.6 (9.90-13.3)	17.2 (15.4-19.3)	24.9 (22.0-30.3)	31.9 (26.4-40.6)	499
Mexican Americans	07-08	10.6 (9.47-11.9)	10.8 (9.70-12.2)	17.1 (14.9-19.2)	26.3 (20.7-30.4)	31.5 (25.7-36.1)	391
Mexican Americans	09-10	6.23 (5.28-7.36)	6.10 (5.10-8.10)	11.2 (8.50-14.1)	16.8 (14.9-18.8)	20.4 (17.5-22.7)	461
Non-Hispanic Blacks	99-00	33.1 (26.5-41.5)	32.0 (24.9-46.7)	51.4 (37.4-62.9)	68.7 (60.4-74.0)	78.3 (70.7-108)	269
Non-Hispanic Blacks	03-04	21.6 (19.1-24.4)	22.1 (19.6-24.9)	32.3 (28.1-36.2)	43.8 (37.2-57.3)	57.7 (43.8-78.4)	538
Non-Hispanic Blacks	05-06	18.4 (15.6-21.8)	19.0 (16.7-22.3)	27.6 (24.3-35.5)	45.9 (34.4-58.1)	57.9 (45.0-84.4)	544
Non-Hispanic Blacks	07-08	15.0 (12.6-17.8)	15.2 (12.9-17.7)	25.8 (21.0-33.3)	42.7 (31.5-57.3)	57.3 (43.4-79.2)	419
Non-Hispanic Blacks	09-10	9.11 (7.93-10.5)	9.50 (8.20-11.2)	16.0 (13.4-17.4)	23.0 (20.5-26.1)	28.7 (25.7-39.7)	391
Non-Hispanic Whites	99-00	32.1 (29.4-35.1)	32.7 (29.5-35.8)	45.3 (40.4-47.6)	56.3 (51.7-67.0)	75.7 (57.1-98.4)	491
Non-Hispanic Whites	03-04	21.4 (19.9-23.1)	22.0 (20.5-23.0)	30.2 (27.7-33.3)	41.7 (35.7-49.6)	56.3 (44.0-70.0)	962
Non-Hispanic Whites	05-06	18.1 (17.1-19.1)	18.6 (17.3-19.8)	28.3 (26.1-30.8)	39.7 (35.6-43.3)	46.6 (42.7-54.3)	935
Non-Hispanic Whites	07-08	13.7 (12.7-14.8)	14.3 (13.2-15.5)	21.1 (18.7-23.7)	32.9 (29.7-36.0)	40.4 (36.1-44.9)	931
Non-Hispanic Whites	09-10	10.2 (8.69-11.9)	10.4 (9.20-11.5)	15.6 (13.0-18.7)	24.7 (17.5-35.1)	33.1 (20.7-56.7)	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, 0.4, 0.2, 0.2, and 0.2 respectively.

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

Factsheet: https://www.cdc.gov/biomonitoring/PFAS_FactSheet.html

Serum Perfluorooctane sulfonic acid (PFOS) (2011 - 2018)

Sum of linear and branched PFOS isomers

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	6.31 (5.84-6.82)	6.53 (5.99-7.13)	10.5 (9.78-11.1)	15.7 (14.7-17.5)	21.7 (19.3-23.9)	1904
Total population	13-14	5.01 (4.53-5.54)	5.30 (4.90-5.70)	8.70 (7.90-9.50)	14.0 (11.9-15.5)	18.5 (15.5-21.6)	1954
Total population	15-16	4.72 (4.40-5.07)	4.80 (4.40-5.30)	8.10 (7.30-9.40)	13.2 (11.4-15.6)	18.3 (15.5-22.7)	1993
Total population	17-18	4.25 (3.90-4.62)	4.30 (3.80-4.90)	7.50 (6.80-8.20)	11.5 (10.0-13.1)	14.6 (13.1-16.5)	1929
Age 12-19 years	11-12	4.16 (3.70-4.68)	4.11 (3.48-4.65)	5.90 (5.14-7.25)	9.05 (6.49-10.8)	10.8 (8.52-14.2)	344
Age 12-19 years	13-14	3.60 (3.24-3.99)	3.60 (3.20-4.20)	5.20 (4.60-6.60)	7.90 (7.10-8.90)	9.00 (8.10-10.8)	348
Age 12-19 years	15-16	2.94 (2.70-3.19)	2.90 (2.70-3.30)	4.30 (3.70-5.00)	6.00 (5.50-6.60)	6.60 (6.10-7.70)	353
Age 12-19 years	17-18	2.68 (2.31-3.12)	2.60 (2.20-3.00)	3.70 (3.10-4.50)	5.70 (4.50-7.30)	7.30 (5.70-10.9)	313
Age 20+ years	11-12	6.71 (6.24-7.20)	7.07 (6.65-7.52)	11.0 (10.4-11.9)	17.0 (15.3-18.5)	22.7 (20.4-24.8)	1560
Age 20+ years	13-14	5.24 (4.72-5.83)	5.60 (5.10-6.00)	9.10 (8.20-10.2)	14.6 (12.9-16.1)	19.3 (16.1-22.7)	1606
Age 20+ years	15-16	5.02 (4.64-5.43)	5.20 (4.80-5.70)	8.80 (7.80-10.2)	14.0 (12.2-16.4)	19.1 (15.8-24.4)	1640
Age 20+ years	17-18	4.50 (4.15-4.89)	4.70 (4.20-5.20)	8.00 (7.20-8.70)	12.2 (10.2-13.4)	15.1 (13.5-17.0)	1616
Males	11-12	7.91 (7.19-8.70)	8.31 (7.35-9.15)	12.5 (11.4-13.5)	19.3 (15.7-21.4)	24.1 (22.2-28.5)	966
Males	13-14	6.37 (5.65-7.17)	6.40 (5.60-7.30)	10.2 (8.80-11.6)	15.4 (13.5-19.1)	21.4 (17.0-26.0)	931
Males	15-16	6.16 (5.66-6.70)	6.40 (5.60-6.70)	10.1 (8.90-11.0)	15.6 (13.2-18.8)	21.3 (17.4-24.4)	964
Males	17-18	5.36 (4.82-5.97)	5.50 (4.90-6.30)	8.80 (7.90-9.80)	12.6 (11.4-14.6)	15.8 (13.6-18.4)	952
Females	11-12	5.10 (4.70-5.53)	5.27 (4.67-5.64)	8.57 (7.87-9.30)	12.5 (11.0-14.9)	17.5 (14.9-20.5)	938
Females	13-14	3.99 (3.62-4.40)	4.10 (3.60-4.60)	7.20 (6.40-7.80)	11.9 (9.60-13.9)	15.1 (14.0-17.4)	1023
Females	15-16	3.67 (3.34-4.03)	3.60 (3.30-3.90)	6.30 (5.50-7.10)	10.9 (9.10-12.7)	14.6 (12.2-18.3)	1029
Females	17-18	3.42 (3.08-3.78)	3.30 (2.90-3.70)	5.70 (5.00-6.70)	9.50 (8.20-11.2)	13.1 (9.80-16.7)	977
Mexican Americans	11-12	4.79 (4.07-5.64)	5.18 (3.92-6.33)	7.91 (6.18-9.48)	10.5 (8.50-12.6)	12.1 (10.0-14.4)	211
Mexican Americans	13-14	3.47 (2.95-4.09)	3.70 (3.00-4.30)	5.20 (4.60-6.20)	8.60 (6.20-10.6)	10.8 (8.80-12.1)	297
Mexican Americans	15-16	3.36 (2.97-3.81)	3.40 (2.80-3.90)	5.80 (4.80-6.60)	8.80 (7.30-9.90)	12.5 (9.50-14.2)	370
Mexican Americans	17-18	2.89 (2.46-3.41)	2.70 (2.30-3.30)	4.90 (3.80-6.20)	7.80 (6.20-9.30)	9.30 (7.80-15.0)	297
Non-Hispanic Blacks	11-12	6.35 (5.41-7.46)	6.57 (5.71-7.65)	11.3 (9.74-13.9)	21.8 (13.9-31.3)	30.7 (21.6-45.1)	485
Non-Hispanic Blacks	13-14	5.40 (4.11-7.10)	5.50 (4.40-7.20)	10.4 (7.60-14.4)	19.1 (12.9-24.9)	24.6 (17.2-39.7)	389
Non-Hispanic Blacks	15-16	4.81 (4.06-5.69)	4.80 (3.90-6.50)	9.70 (8.10-11.2)	17.7 (13.1-22.0)	23.8 (21.8-34.0)	439
Non-Hispanic Blacks	17-18	4.23 (3.60-4.98)	4.00 (3.40-4.90)	7.80 (6.10-9.80)	15.3 (10.5-19.3)	21.9 (17.2-32.2)	430
Non-Hispanic Whites	11-12	6.71 (6.15-7.32)	6.83 (6.07-7.73)	10.7 (9.89-12.2)	15.7 (14.8-18.1)	21.3 (18.7-23.5)	666
Non-Hispanic Whites	13-14	5.32 (4.75-5.97)	5.70 (5.10-6.40)	9.00 (8.10-9.90)	14.1 (12.2-15.5)	17.9 (15.4-20.3)	805
Non-Hispanic Whites	15-16	4.97 (4.67-5.29)	5.10 (4.60-5.60)	8.30 (7.40-9.90)	13.2 (11.3-15.5)	17.4 (14.2-21.3)	619
Non-Hispanic Whites	17-18	4.65 (4.32-5.01)	4.90 (4.30-5.30)	8.10 (7.20-9.00)	11.5 (10.1-13.1)	13.9 (13.0-15.7)	667
All Hispanics	11-12	4.63 (3.86-5.55)	5.18 (4.41-6.19)	8.10 (6.64-9.78)	11.0 (9.96-12.6)	13.4 (11.5-16.1)	406
All Hispanics	13-14	3.52 (3.12-3.96)	3.70 (3.20-4.30)	5.50 (5.00-6.40)	8.80 (7.90-9.50)	10.9 (9.60-12.1)	488
All Hispanics	15-16	3.57 (3.14-4.06)	3.60 (3.00-4.30)	6.30 (5.40-7.10)	9.50 (8.00-11.8)	13.0 (10.5-15.2)	629
All Hispanics	17-18	3.18 (2.75-3.67)	3.10 (2.70-3.70)	5.40 (4.40-6.40)	8.20 (7.40-8.80)	10.0 (8.40-13.2)	473
Asians	11-12	7.10 (5.80-8.68)	7.53 (5.96-9.25)	12.6 (10.8-17.0)	24.6 (19.1-33.3)	35.1 (26.4-42.3)	291
Asians	13-14	6.30 (5.18-7.66)	6.30 (5.00-7.90)	13.2 (9.40-15.2)	24.3 (14.2-36.5)	33.6 (19.0-78.2)	203
Asians	15-16	5.75 (4.37-7.58)	5.30 (4.20-7.00)	10.5 (7.40-17.6)	25.2 (10.4-52.3)	34.8 (13.9-84.3)	220
Asians	17-18	4.36 (3.40-5.59)	4.20 (3.20-6.10)	8.20 (6.20-12.2)	17.3 (10.8-26.2)	25.5 (16.0-32.0)	257

Limit of detection (LOD, see Data Analysis section) for Survey year 11-12 is 0.2.

‡See Calculation of PFOS and PFOA as the Sum of Isomers for additional information about Survey years 2013-2014, 2015-2016, and 2017-2018.

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

Serum estimated PFOS (total) (Special Sample of Serum PFAS in Children, 2013-2014)

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	3.90 (3.49-4.35)	3.84 (3.39-4.26)	5.77 (4.88-6.43)	8.37 (6.98-11.0)	11.8 (9.03-13.1)	525
Age 3-5 years	13-14	3.37 (2.99-3.79)	3.39 (2.64-3.98)	4.78 (3.98-6.32)	7.18 (4.78-8.66)	9.10 (7.18-11.3)	149
Age 6-11 years	13-14	4.18 (3.70-4.72)	4.00 (3.44-4.57)	5.91 (5.02-6.75)	9.32 (6.75-12.4)	12.4 (9.38-14.4)	376
Males	13-14	4.05 (3.45-4.74)	4.07 (3.25-4.88)	6.32 (5.09-7.18)	9.03 (6.93-12.8)	12.4 (8.66-17.3)	284
Females	13-14	3.73 (3.36-4.15)	3.53 (3.09-4.03)	5.01 (4.30-6.19)	7.37 (6.39-9.24)	9.61 (7.17-12.4)	241
All Hispanics	13-14	3.52 (3.08-4.02)	3.41 (2.89-3.93)	4.74 (4.13-5.67)	7.61 (5.29-9.54)	9.32 (6.25-11.0)	186
Other	13-14	4.03 (3.58-4.54)	3.98 (3.40-4.57)	6.19 (5.02-6.75)	9.03 (6.98-12.0)	12.4 (9.17-14.6)	339

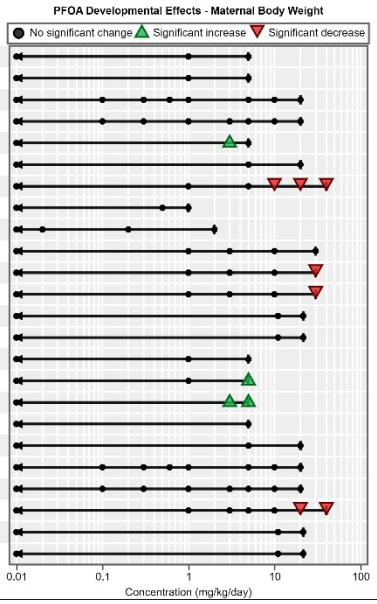
* See Calculation of PFOS and PFOA as the Sum of Isomers for additional information about Survey years 2013-2014.

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

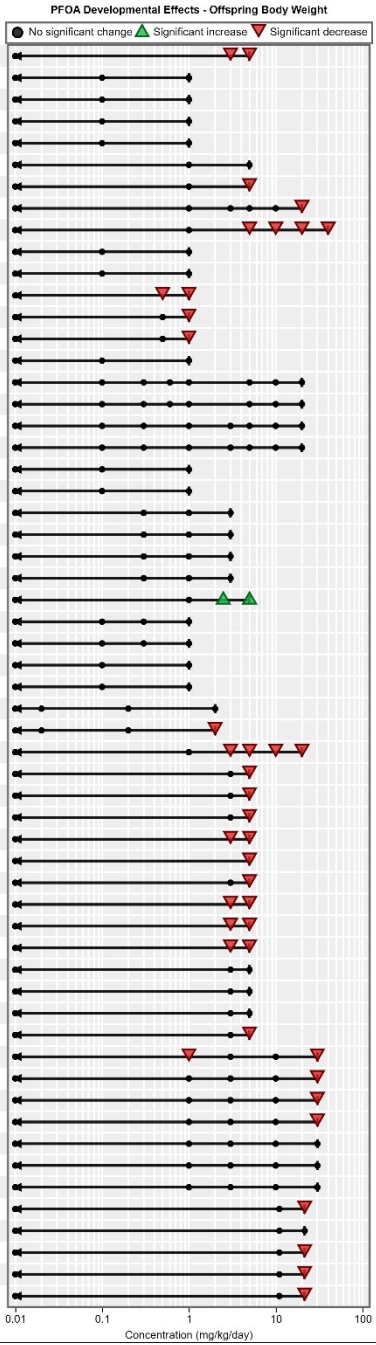
Appendix 5 Developmental and Reproductive Data Visualizations for Animal Studies (USEPA 2024a,b)

5.1 PFOA Developmental Endpoints

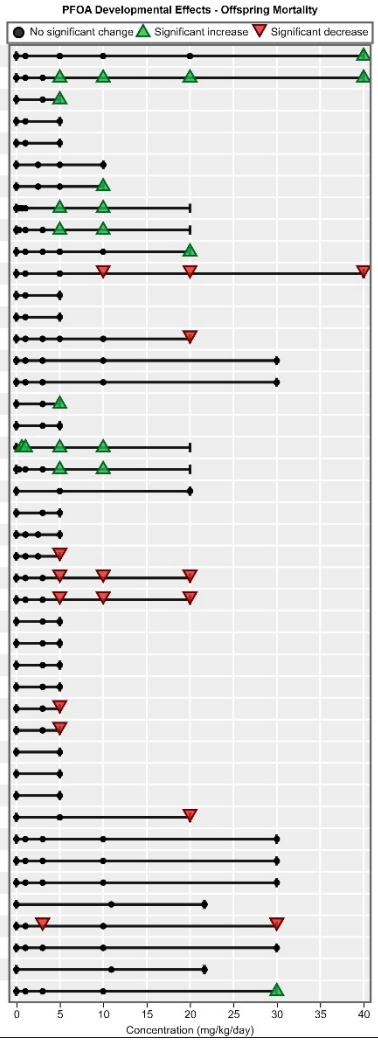
Endpoint	Study Name	Study Design	Observation Time	Animal Description
Maternal Body Weight	Blake et al., 2020, 6305864	developmental (GD1.5-11.5)	GD11.5	P0 Mouse, CD-1 (♀, N=11)
		developmental (GD1.5-17.5)	GD17.5	P0 Mouse, CD-1 (♀, N=11)
	Abbott et al., 2007, 1335452	developmental (GD1-17)	GD17	P0 Mouse, 129S1/SvImJ (♀, N=0-21)
				P0 Mouse, 129S4/SvJae PPARα null (♂, N=1-19)
	Wolf et al., 2007, 1332672	developmental (GD1-17)	GD17	P0 Mouse, CD-1 (♀, N=25-39)
		developmental (GD15-17)	GD17	P0 Mouse, CD-1 (♀, N=4-10)
	Li et al., 2018, 5084746	developmental (GD1-17)	GD18	P0 Mouse, Kunming (♂, N=10)
	Hu et al., 2010, 1332421	developmental (GD6-17)	GD19	P0 Mouse, C57BL/6n (♂, N=16)
	Hu et al., 2012, 1937235	developmental (14d mating-PND21)	PND21	P0 Mouse, C57Bl6/N (♀, N=24)
	Butenhoff et al., 2004, 1291063	reproductive (84d)	LD22	P0 Rat, Crl:CD(SD)IGS BR (♀, N=26-29)
		reproductive (GD1-PND106)	GD14	F1 Rat, Crl:CD(SD)IGS BR (♀, N=28-29)
			LD15	F1 Rat, Crl:CD(SD)IGS BR (♀, N=28-29)
	NTP, 2020, 7330145	chronic (GD6-PND21)	GD21	P0 Rat, Sprague-Dawley (♀, N=30-91)
			LD21	P0 Rat, Sprague-Dawley (♀, N=30-86)
Maternal Body Weight Change	Blake et al., 2020, 6305864	developmental (GD1.5-11.5)	GD0.5-11.5	P0 Mouse, CD-1 (♀, N=11)
		developmental (GD1.5-17.5)	GD0.5-17.5	P0 Mouse, CD-1 (♀, N=11)
	Wolf et al., 2007, 1332672	developmental (GD1-17)	GD1-17	P0 Mouse, CD-1 (♂, N=25-39)
		developmental (GD13-17)	GD1-17	P0 Mouse, CD-1 (♂, N=8-12)
		developmental (GD15-17)	GD1-17	P0 Mouse, CD-1 (♀, N=4-10)
	Abbott et al., 2007, 1335452	developmental (GD1-17)	GD1-17	P0 Mouse, 129S1/SvImJ (♀, N=0-21)
				P0 Mouse, 129S4/SvJae PPARα null (♂, N=1-19)
	Lau et al., 2006, 1276159	developmental (GD1-17)	GD18	P0 Mouse, CD-1 (♀, N=9-45)
	NTP, 2020, 7330145	chronic (GD6-PND21)	GD6-21	P0 Rat, Sprague-Dawley (♀, N=30-91)
			LD1-21	P0 Rat, Sprague-Dawley (♀, N=30-86)



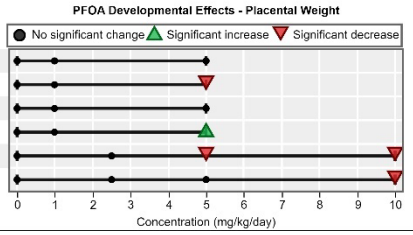
Endpoint	Study Name	Study Design	Observation Time	Animal Description
Body Weight Change	Wolf et al., 2007, 1332672	developmental (GD1-17)	PND1-22	F1 Mouse, CD-1 (♂♀, N=11-14)
	Cope et al., 2021, 10176465	developmental (GD1.5-17.5)	PND22-PNW18	F1 Mouse, CD-1 (♂, N=8)
				F1 Mouse, CD-1 (♀, N=9)
			PND22-128	F1 Mouse, CD-1 (♂)
				F1 Mouse, CD-1 (♀)
Fetal Body Weight	Blake et al., 2020, 6305864	developmental (GD1.5-11.5)	GD11.5	F1 Mouse, CD-1 (♂♀, N=62)
		developmental (GD1.5-17.5)	GD17.5	F1 Mouse, CD-1 (♂♀, N=62)
	Lau et al., 2006, 1276159	developmental (GD1-17)	GD18	F1 Mouse, CD-1 (♂♀, N=5-42)
	Li et al., 2018, 5084746	developmental (GD1-17)	GD18	F1 Mouse, Kunming (♂♀, N=10)
Litter Weight	Cope et al., 2021, 10176465	developmental (GD1.5-17.5)	PND0.5	F1 Mouse, CD-1 (♂♀, N=9)
			PND5.5	F1 Mouse, CD-1 (♂♀, N=9)
	Hu et al., 2010, 1332421	developmental (GD6-17)	PND2	F1 Mouse, C57BL/6n (♂♀, N=10)
			PND7	F1 Mouse, C57BL/6n (♂♀, N=10)
			PND14	F1 Mouse, C57BL/6n (♂♀, N=10)
Pup Body Weight	Cope et al., 2021, 10176465	developmental (GD1.5-17.5)	PND0.5	P0 Mouse, CD-1 (♀, N=9)
	Abbott et al., 2007, 1335452	developmental (GD1-17)	PND1	F1 Mouse, 129S1/SvImJ (♀, N=0-18)
				F1 Mouse, 129S1/SvImJ (♂, N=0-17)
				F1 Mouse, 129S4/SvJae PPARα null (♀, N=0-18)
				F1 Mouse, 129S4/SvJae PPARα null (♂, N=0-17)
	Macon et al., 2011, 1276151	developmental (GD10-17)	PND1	F1 Mouse, CD-1 (♀, N=7-9)
			PND21	F1 Mouse, CD-1 (♀, N=7-11)
		developmental (GD1-17)	PND7	F1 Mouse, CD-1 (♂, N=3-6)
				F1 Mouse, CD-1 (♀, N=4-5)
			PND21	F1 Mouse, CD-1 (♂, N=4)
				F1 Mouse, CD-1 (♀, N=3-6)
	Song et al., 2018, 5079725	developmental (GD1-17)	PND21	F1 Mouse, Kunming (♂, N=9-10)
	Tucker et al., 2015, 2851046	developmental (GD1–17)	PND21	F1 Mouse, C57Bl/6 (♀, N=2-6)
				F1 Mouse, CD-1 (♀, N=20-22)
Pup Weight Relative to Litter	Cope et al., 2021, 10176465	developmental (GD1.5-17.5)	PND 0.5	F1 Mouse, CD-1 (♂♀, N=9)
			PND5.5	F1 Mouse, CD-1 (♂♀, N=9)
	Hu et al., 2012, 1937235	developmental (14d mating-PND21)	PND1	F1 Mouse, C57Bl6/N (♂♀, N=11-14)
			PND21	F1 Mouse, C57Bl6/N (♂♀, N=7-11)
	Lau et al., 2006, 1276159	developmental (GD1-18)	PND22	F1 Mouse, CD-1 (♂♀, N=7-23)
	Wolf et al., 2007, 1332672	developmental (GD1-17)	PND1	F1 Mouse, CD-1 (♂, N=11-14)
				P0 Mouse, CD-1 (♀, N=25-39)
				F1 Mouse, CD-1 (♀, N=11-14)
			PND22	F1 Mouse, CD-1 (♂, N=11-14)
		developmental (GD7-17)	PND22	F1 Mouse, CD-1 (♂, N=7-13)
		developmental (GD1-PND22)	PND1	F1 Mouse, CD-1 (♂, N=12-14)
				F1 Mouse, CD-1 (♂, N=12-14)
			PND22	F1 Mouse, CD-1 (♂, N=12-14)
				F1 Mouse, CD-1 (♀, N=12-14)
		developmental (PND1-22)	PND1	F1 Mouse, CD-1 (♂, N=11-14)
				F1 Mouse, CD-1 (♀, N=11-14)
			PND22	F1 Mouse, CD-1 (♂, N=11-14)
				F1 Mouse, CD-1 (♀, N=11-14)
	Butenhoff et al., 2004, 1291063	reproductive (84d)	PND1	F1 Rat, Crl:CD(SD)IGS BR (♂♀, N=27-29)
			PND5	F1 Rat, Crl:CD(SD)IGS BR (♂♀, N=27-29)
			PND8	F1 Rat, Crl:CD(SD)IGS BR (♂♀, N=27-29)
			PND15	F1 Rat, Crl:CD(SD)IGS BR (♂♀, N=27-29)
			PND22	F1 Rat, Crl:CD(SD)IGS BR (♂♀, N=27-29)
		reproductive (GD1-PND106)	PND1	F2 Rat, Crl:CD(SD)IGS BR (♂♀, N=29-30)
			PND22	F2 Rat, Crl:CD(SD)IGS BR (♂♀, N=29-30)
	NTP, 2020, 7330145	chronic (GD6-PND21)	PND1	F1 Rat, Sprague-Dawley (♂♀, N=31-90)
			PND4	F1 Rat, Sprague-Dawley (♂♀, N=30-86)
			PND7	F1 Rat, Sprague-Dawley (♂♀, N=30-86)
			PND14	F1 Rat, Sprague-Dawley (♂♀, N=30-86)
			PND21	F1 Rat, Sprague-Dawley (♂♀, N=30-86)



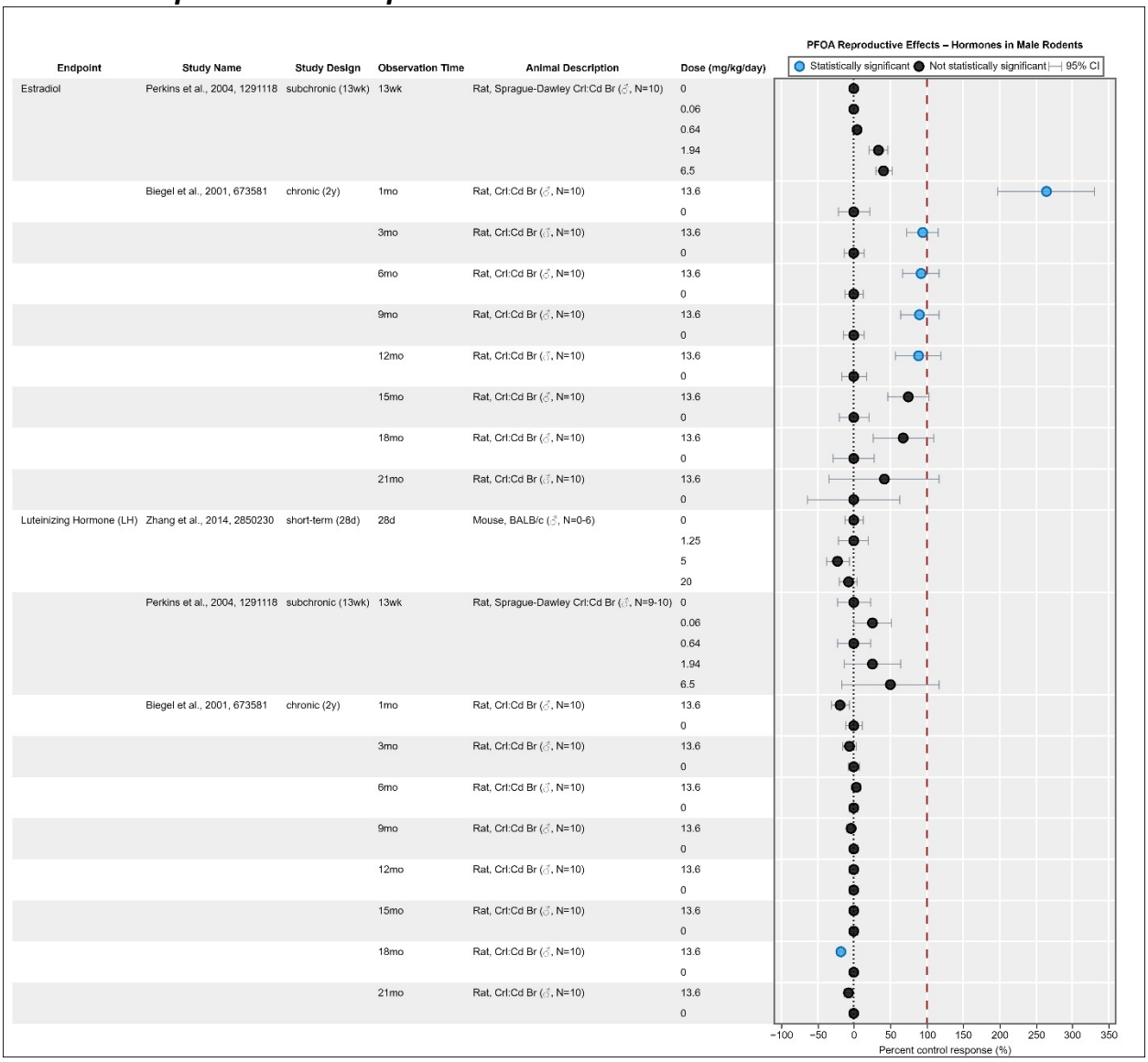
Endpoint	Study Name	Study Design	Observation Time	Animal Description
Full Litter Resorption (%)	Li et al., 2018, 5084746	developmental (GD1-17)	GD18	P0 Mouse, Kunming (♀, N=10)
	Lau et al., 2006, 1276159	developmental (GD1-17)	GD18	P0 Mouse, CD-1 (♀, N=9-45)
	Wolf et al., 2007, 1332672	developmental (GD1-17)	PND1	P0 Mouse, CD-1 (♀, N=25-39)
Resorptions, Mean/Litter	Blake et al., 2020, 6305864	developmental (GD1.5-11.5)	GD11.5	P0 Mouse, CD-1 (♀, N=11)
		developmental (GD1.5-17.5)	GD17.5	P0 Mouse, CD-1 (♀, N=11)
Resorptions, Early	Chen et al., 2017, 3981369	developmental (GD1-7)	GD7	P0 Mouse, Kunming (♀, N=6)
Resorptions, Late	Chen et al., 2017, 3981369	developmental (GD1-13)	GD13	P0 Mouse, Kunming (♀, N=6)
Resorptions, Percent Dams	Abbott et al., 2007, 1335452	developmental (GD1-17)	GD17	P0 Mouse, 129S1/SvImJ (♀, N=5-22)
				P0 Mouse, 129S4/SvJae PPARα null (♀, N=4-23)
Prenatal Loss (% per Live Litter)	Lau et al., 2006, 1276159	developmental (GD1-17)	GD18	P0 Mouse, CD-1 (♀, N=5-42)
Fetal Survival	Li et al., 2018, 5084746	developmental (GD1-17)	GD18	P0 Mouse, Kunming (♀, N=10)
Fetuses, Dead	Blake et al., 2020, 6305864	developmental (GD1.5-11.5)	GD11.5	P0 Mouse, CD-1 (♀, N=11)
		developmental (GD1.5-17.5)	GD17.5	P0 Mouse, CD-1 (♀, N=11)
Fetuses, Live (No. per Live Litter)	Lau et al., 2006, 1276159	developmental (GD1-17)	GD18	P0 Mouse, CD-1 (♀, N=5-42)
Stillborn Pups, Mean/Litter	Butenhoff et al., 2004, 1291063	reproductive (84d)	PND0	F1 Rat, Crl:CD(SD)IGS BR (♂♀, N=27-29)
		reproductive (GD1-PND106)	PND0	F2 Rat, Crl:CD(SD)IGS BR (♂♀, N=29-30)
Dams with Whole Litter Loss (%)	Wolf et al., 2007, 1332672	developmental (GD1-17)	PND1	P0 Mouse, CD-1 (♀, N=28-48)
Litter Loss (% per Live Litter)	Wolf et al., 2007, 1332672	developmental (GD1-17)	PND1	P0 Mouse, CD-1 (♀, N=24-38)
Litter Loss (%)	Abbott et al., 2007, 1335452	developmental (GD1-17)	GD17	P0 Mouse, 129S1/SvImJ (♀, N=5-22)
				P0 Mouse, 129S4/SvJae PPARα null (♀, N=4-23)
	Wolf et al., 2007, 1332672	developmental (GD15-17)	PND22	P0 Mouse, CD-1 (♀, N=4-10)
Live Pups Born (No. per Live Litter)	Wolf et al., 2007, 1332672	developmental (GD1-17)	PND1	P0 Mouse, CD-1 (♀, N=25-39)
Offspring Survival	Song et al., 2018, 5079725	developmental (GD1-17)	PND0	F1 Mouse, Kunming (♂♀, N=10)
			PND21	F1 Mouse, Kunming (♂♀, N=10)
	Lau et al., 2006, 1276159	developmental (GD1-18)	PND0	F1 Mouse, CD-1 (♂♀, N=8)
			PND22	F1 Mouse, CD-1 (♂♀, N=8)
	Wolf et al., 2007, 1332672	developmental (GD1-17)	PND4	F1 Mouse, CD-1 (♂♀)
			PND22	F1 Mouse, CD-1 (♂♀)
		developmental (PND1-22)	PND4	F1 Mouse, CD-1 (♂♀)
			PND22	F1 Mouse, CD-1 (♂♀)
		developmental (GD1-PND22)	PND4	F1 Mouse, CD-1 (♂♀)
			PND22	F1 Mouse, CD-1 (♂♀)
		developmental (GD7-17)	PND1-22	F1 Mouse, CD-1 (♂♀, N=7-13)
		developmental (GD10-17)	PND1-22	F1 Mouse, CD-1 (♂♀, N=7-13)
		developmental (GD13-17)	PND1-22	F1 Mouse, CD-1 (♂♀, N=7-10)
		developmental (GD15-17)	PND1-22	F1 Mouse, CD-1 (♂♀, N=3-10)
Pre-Weaning Mortality (%)	Butenhoff et al., 2004, 1291063	reproductive (84d)	PND1-22	F1 Rat, Crl:CD(SD)IGS BR (♂♀, N=27-29)
Viability Index	Butenhoff et al., 2004, 1291063	reproductive (84d)	PND5	F1 Rat, Crl:CD(SD)IGS BR (♂♀, N=27-29)
		reproductive (GD1-PND106)	PND5	F2 Rat, Crl:CD(SD)IGS BR (♂♀, N=29-30)
	NTP, 2020, 7330145	chronic (GD6-PND21)	PND4	F1 Rat, Sprague-Dawley (♂♀, N=31-90)
Lactation Index	Butenhoff et al., 2004, 1291063	reproductive (84d)	PND22	F1 Rat, Crl:CD(SD)IGS BR (♂♀, N=27-29)
		reproductive (GD1-PND106)	PND22	F2 Rat, Crl:CD(SD)IGS BR (♂♀, N=29-30)
	NTP, 2020, 7330145	chronic (GD6-PND21)	PND21	F1 Rat, Sprague-Dawley (♂♀, N=30-86)
Post-Weaning Mortality (%)	Butenhoff et al., 2004, 1291063	reproductive (84d)	PND22-60	F1 Rat, Crl:CD(SD)IGS BR (♀, N=60)

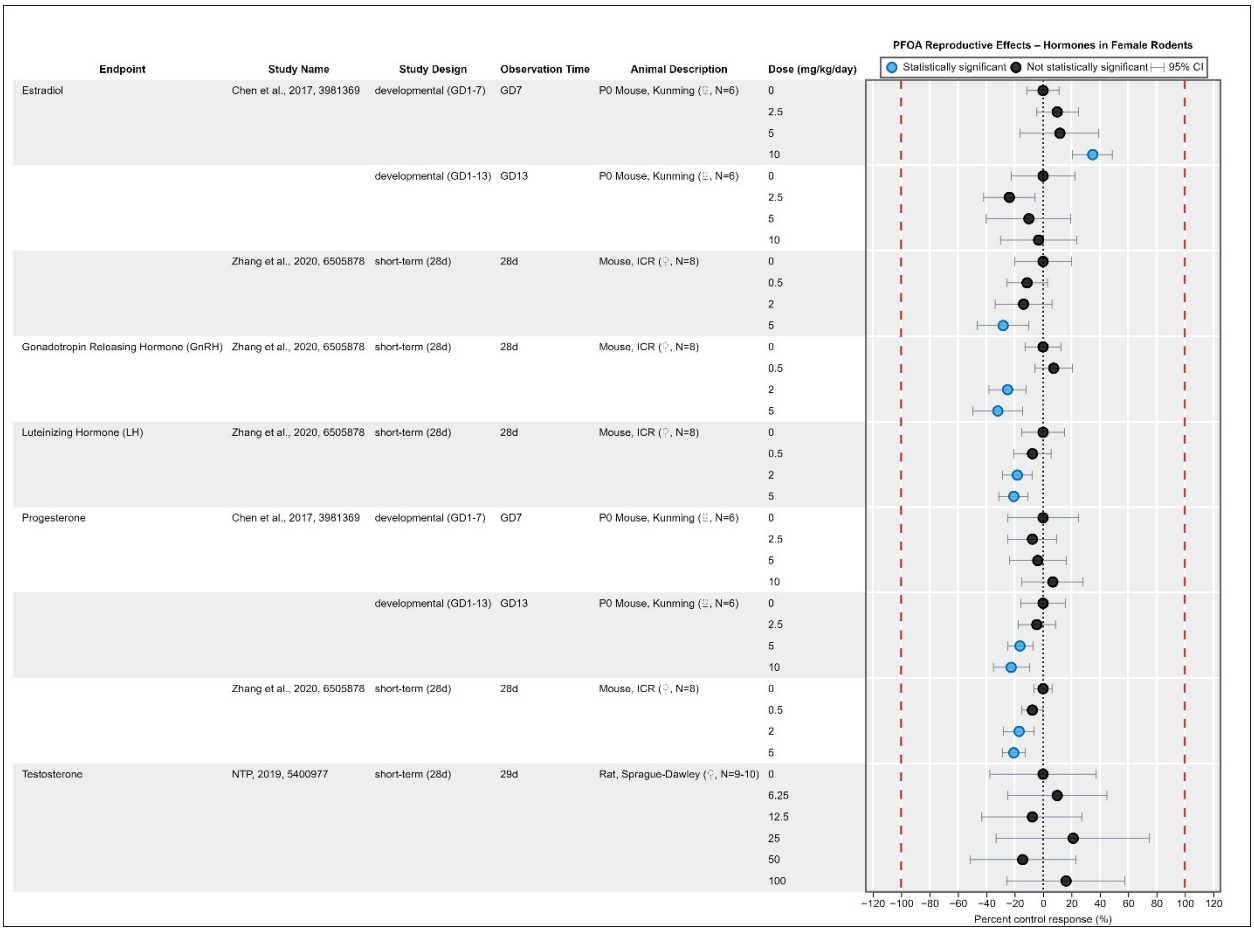


Endpoint	Study Name	Study Design	Observation Time	Animal Description
Embryo:Placenta Weight Ratio	Blake et al., 2020, 6305864	developmental (GD1.5-11.5)	GD11.5	P0 Mouse, CD-1 (♀, N=62)
		developmental (GD1.5-17.5)	GD17.5	P0 Mouse, CD-1 (♀, N=62)
Placenta Weight, Absolute	Blake et al., 2020, 6305864	developmental (GD1.5-11.5)	GD11.5	P0 Mouse, CD-1 (♀, N=62)
		developmental (GD1.5-17.5)	GD17.5	P0 Mouse, CD-1 (♀, N=62)
Placenta Weight, Relative	Jiang et al., 2020, 6320192	developmental (GD1-13)	GD13	P0 Mouse, Kunming (♀, N=6)
Placenta and Embryo Weight, Relative	Jiang et al., 2020, 6320192	developmental (GD1-13)	GD13	P0 Mouse, Kunming (♀, N=6)

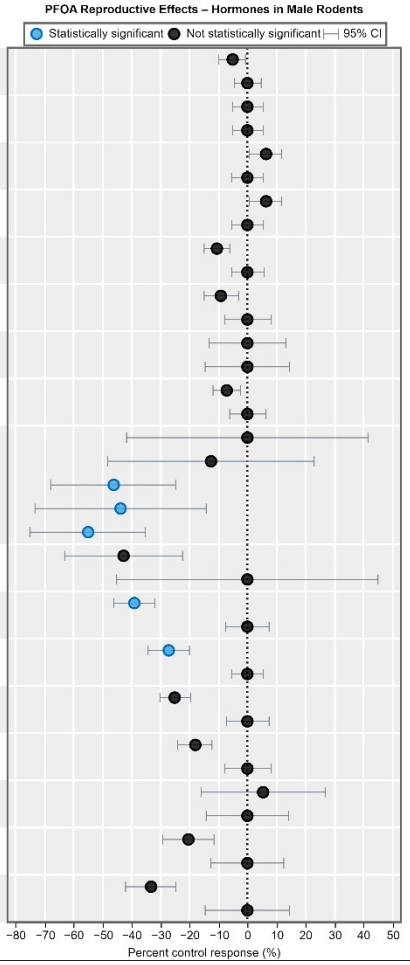


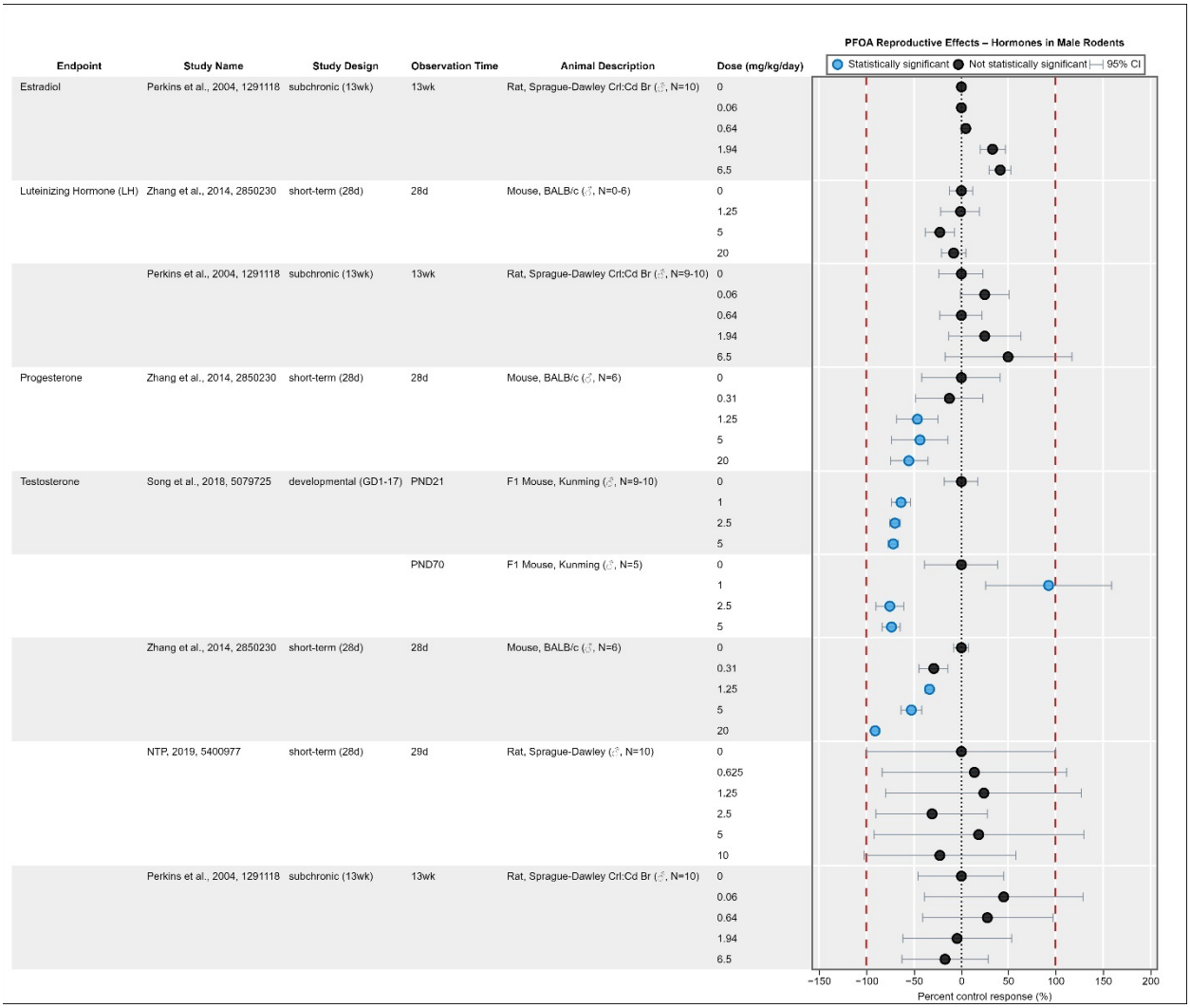
5.2 PFOA Reproductive Endpoints



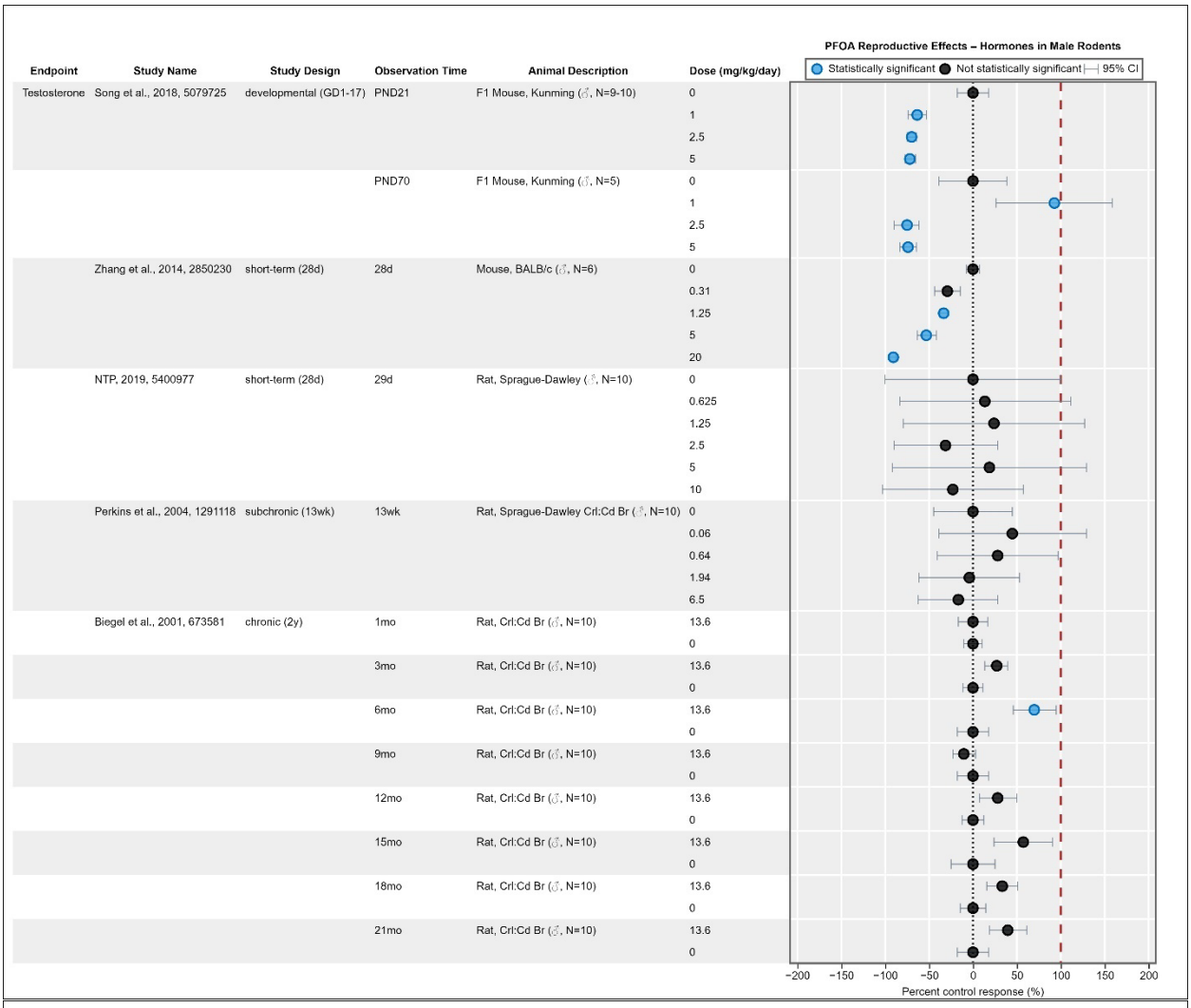

PFOA Reproductive Effects – Hormones in Female Rodents
Statistically significant
Not statistically significant
95% CI
Endpoint
Study Name
Study Design
Observation Time
Animal Description
Dose (mg/kg/day)
Estradiol
Chen et al., 2017, 3981369
developmental (GD1-7)
GD7
P0 Mouse, Kunming (♀, N=6)
0
2.5
5
10
developmental (GD1-13)
GD13
P0 Mouse, Kunming (♀, N=6)
0
2.5
5
10
Zhang et al., 2020, 6505878
short-term (28d)
28d
Mouse, ICR (♀, N=8)
0
0.5
2
5
Gonadotropin Releasing Hormone (GnRH)
Zhang et al., 2020, 6505878
short-term (28d)
28d
Mouse, ICR (♀, N=8)
0
0.5
2
5
Luteinizing Hormone (LH)
Zhang et al., 2020, 6505878
short-term (28d)
28d
Mouse, ICR (♀, N=8)
0
0.5
2
5
Progesterone
Chen et al., 2017, 3981369
developmental (GD1-7)
GD7
P0 Mouse, Kunming (♀, N=6)
0
2.5
5
10
developmental (GD1-13)
GD13
P0 Mouse, Kunming (♀, N=6)
0
2.5
5
10
Zhang et al., 2020, 6505878
short-term (28d)
28d
Mouse, ICR (♀, N=8)
0
0.5
2
5
Testosterone
NTP, 2019, 5400977
short-term (28d)
29d
Rat, Sprague-Dawley (♀, N=9-10)
0
6.25
12.5
25
50
100
−120 −100 −80 −60 −40 −20 0 20 40 60 80 100 120
Percent control response (%)

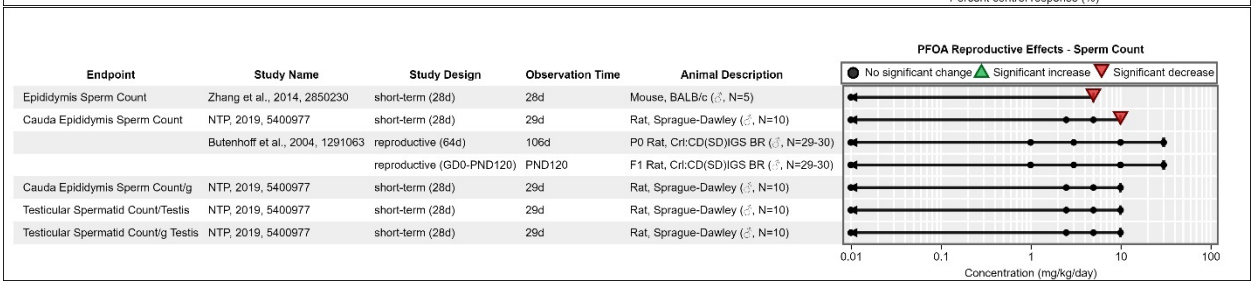
Endpoint	Study Name	Study Design	Observation Time	Animal Description	Dose (mg/kg/day)
Follicle stimulating hormone (FSH)	Biegel et al., 2001, 673581	chronic (2y)	1mo	Rat, Crl:Cd Br (♂, N=10)	13.6
					0
			3mo	Rat, Crl:Cd Br (♂, N=10)	13.6
					0
			6mo	Rat, Crl:Cd Br (♂, N=10)	13.6
					0
			9mo	Rat, Crl:Cd Br (♂, N=10)	13.6
					0
			12mo	Rat, Crl:Cd Br (♂, N=10)	13.6
					0
			15mo	Rat, Crl:Cd Br (♂, N=10)	13.6
					0
			18mo	Rat, Crl:Cd Br (♂, N=10)	13.6
					0
			21mo	Rat, Crl:Cd Br (♂, N=10)	13.6
					0
Progesterone	Zhang et al., 2014, 2850230	short-term (28d)	28d	Mouse, BALB/c (♂, N=6)	0
					0.31
					1.25
					5
					20
Prolactin (PRL)	Biegel et al., 2001, 673581	chronic (2y)	1mo	Rat, Crl:Cd Br (♂, N=10)	13.6
					0
			3mo	Rat, Crl:Cd Br (♂, N=10)	13.6
					0
			6mo	Rat, Crl:Cd Br (♂, N=10)	13.6
					0
			9mo	Rat, Crl:Cd Br (♂, N=10)	13.6
					0
			12mo	Rat, Crl:Cd Br (♂, N=10)	13.6
					0
			15mo	Rat, Crl:Cd Br (♂, N=10)	13.6
					0
			18mo	Rat, Crl:Cd Br (♂, N=10)	13.6
					0
			21mo	Rat, Crl:Cd Br (♂, N=10)	13.6
					0





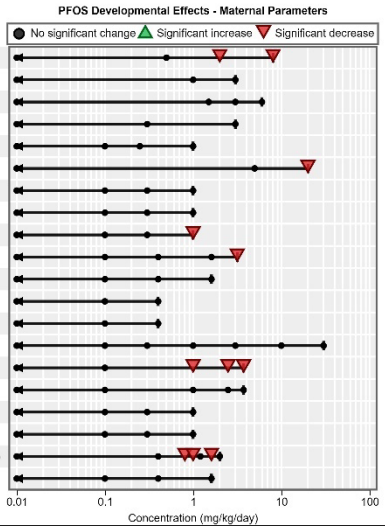
Endpoint	Study Name	Study Design	Observation Time	Animal Description	Dose (mg/kg/day)
Estradiol	Perkins et al., 2004, 1291118	subchronic (13wk)	13wk	Rat, Sprague-Dawley Crl:Cd Br (♂, N=10)	0
					0.06
					0.64
					1.94
					6.5
Luteinizing Hormone (LH)	Zhang et al., 2014, 2850230	short-term (28d)	28d	Mouse, BALB/c (♂, N=0-6)	0
					1.25
					5
					20
	Perkins et al., 2004, 1291118	subchronic (13wk)	13wk	Rat, Sprague-Dawley Crl:Cd Br (♂, N=9-10)	0
					0.06
					0.64
					1.94
					6.5
Progesterone	Zhang et al., 2014, 2850230	short-term (28d)	28d	Mouse, BALB/c (♂, N=6)	0
					0.31
					1.25
					5
					20
Testosterone	Song et al., 2018, 5079725	developmental (GD1-17)	PND21	F1 Mouse, Kunming (♂, N=9-10)	0
					1
					2.5
					5
			PND70	F1 Mouse, Kunming (♂, N=5)	0
					1
					2.5
					5
	Zhang et al., 2014, 2850230	short-term (28d)	28d	Mouse, BALB/c (♂, N=6)	0
					0.31
					1.25
					5
					20
	NTP, 2019, 5400977	short-term (28d)	29d	Rat, Sprague-Dawley (♂, N=10)	0
					0.625
					1.25
					2.5
					5
					10
	Perkins et al., 2004, 1291118	subchronic (13wk)	13wk	Rat, Sprague-Dawley Crl:Cd Br (♂, N=10)	0
					0.06
					0.64
					1.94
					6.5


PFOA Reproductive Effects – Hormones in Male Rodents
Statistically significant
Not statistically significant
95% CI
Endpoint
Study Name
Study Design
Observation Time
Animal Description
Dose (mg/kg/day)
Testosterone
Song et al., 2018, 5079725
developmental (GD1-17)
PND21
F1 Mouse, Kunming (♂, N=9-10)
0
1
2.5
5
PND70
F1 Mouse, Kunming (♂, N=5)
0
1
2.5
5
Zhang et al., 2014, 2850230
short-term (28d)
28d
Mouse, BALB/c (♂, N=6)
0
0.31
1.25
5
20
NTP, 2019, 5400977
short-term (28d)
29d
Rat, Sprague-Dawley (♂, N=10)
0
0.625
1.25
2.5
5
10
Perkins et al., 2004, 1291118
subchronic (13wk)
13wk
Rat, Sprague-Dawley Crl:Cd Br (♂, N=10)
0
0.06
0.64
1.94
6.5
Biegel et al., 2001, 673581
chronic (2y)
1mo
Rat, Crl:Cd Br (♂, N=10)
13.6
0
3mo
Rat, Crl:Cd Br (♂, N=10)
13.6
0
6mo
Rat, Crl:Cd Br (♂, N=10)
13.6
0
9mo
Rat, Crl:Cd Br (♂, N=10)
13.6
0
12mo
Rat, Crl:Cd Br (♂, N=10)
13.6
0
15mo
Rat, Crl:Cd Br (♂, N=10)
13.6
0
18mo
Rat, Crl:Cd Br (♂, N=10)
13.6
0
21mo
Rat, Crl:Cd Br (♂, N=10)
13.6
0
−200
−150
−100
−50
0
50
100
150
200
Percent control response (%)

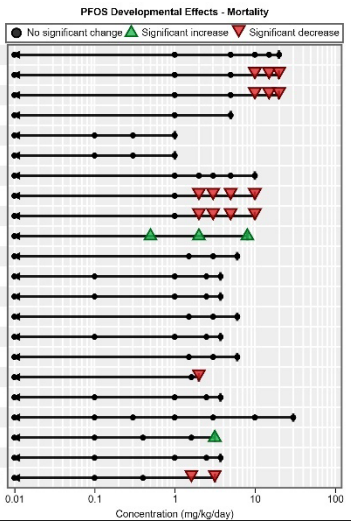

PFOA Reproductive Effects - Sperm Count
No significant change
Significant increase
Significant decrease
Endpoint
Study Name
Study Design
Observation Time
Animal Description
Epididymis Sperm Count
Zhang et al., 2014, 2850230
short-term (28d)
28d
Mouse, BALB/c (♂, N=5)
Cauda Epididymis Sperm Count
NTP, 2019, 5400977
short-term (28d)
29d
Rat, Sprague-Dawley (♂, N=10)
Butenhoff et al., 2004, 1291063
reproductive (64d)
106d
P0 Rat, Crl:CD(SD)IGS BR (♂, N=29-30)
reproductive (GD0-PND120)
PND120
F1 Rat, Crl:CD(SD)IGS BR (♂, N=29-30)
Cauda Epididymis Sperm Count/g
NTP, 2019, 5400977
short-term (28d)
29d
Rat, Sprague-Dawley (♂, N=10)
Testicular Spermatid Count/Testis
NTP, 2019, 5400977
short-term (28d)
29d
Rat, Sprague-Dawley (♂, N=10)
Testicular Spermatid Count/g Testis
NTP, 2019, 5400977
short-term (28d)
29d
Rat, Sprague-Dawley (♂, N=10)
0.01
0.1
1
10
100
Concentration (mg/kg/day)

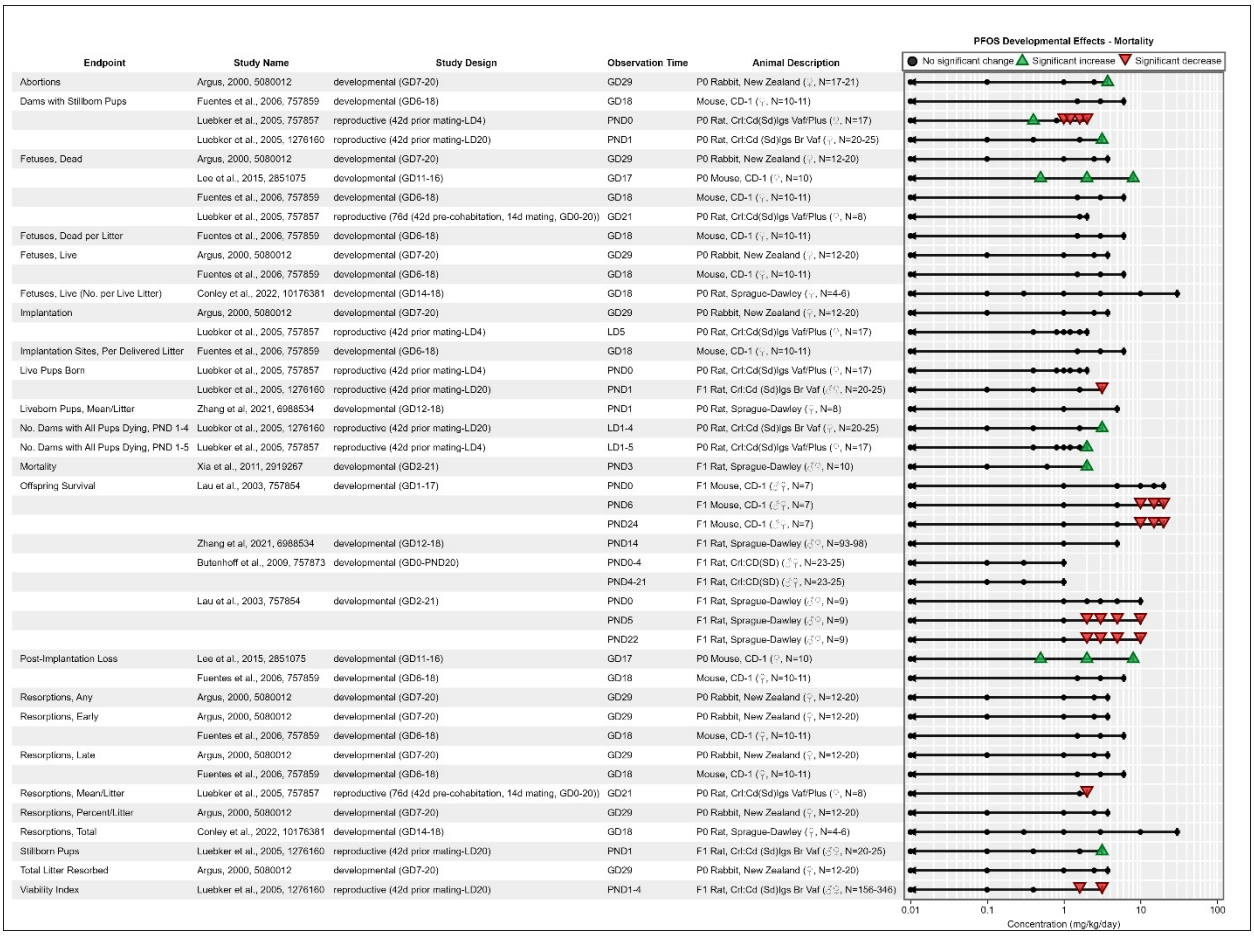
5.3 PFOS Developmental Endpoints

Endpoint	Study Name	Study Design	Observation Time	Animal Description
Maternal Body Weight	Lee et al., 2015, 2851075	developmental (GD11-16)	GD17	P0 Mouse, CD-1 (♀, N=10)
	Wan et al., 2020, 7174720	developmental (GD4.5-17.5)	GD17.5	P0 Mouse, CD-1 (♀, N=8)
	Fuentes et al., 2006, 757859	developmental (GD6-18)	GD18	Mouse, CD-1 (♂, N=10-11)
	Lai et al., 2017, 3981773	developmental (GD1-17)	GD1-20	P0 Mouse, CD-1 (♀, N=6)
	Mshaty et al., 2020, 6833692	developmental (LD1-14)	PND21	P0 Mouse, C57BL/6J (♀, N=0-15)
	Li et al., 2016, 3981495	developmental (GD12-18)	GD18	P0 Rat, Sprague-Dawley (♀, N=10)
	Butenhoff et al., 2009, 757873	developmental (GD0-PND20)	GD20	P0 Rat, Crl:CD(SD) (♀, N=23-25)
			PND1	P0 Rat, Crl:CD(SD) (♀, N=23-25)
			PND21	P0 Rat, Crl:CD(SD) (♂, N=23-25)
	Luebker et al., 2005, 1276160	reproductive (42d prior mating-LD20)	LD1	P0 Rat, Crl:Cd (Sd)Igs Br Vaf (♀, N=24-25)
			LD21	P0 Rat, Crl:Cd (Sd)Igs Br Vaf (♀, N=22-25)
		reproductive (GD0-PND112)	LD1	F1 Rat, Crl:Cd (Sd)Igs Br Vaf (♂, N=22-25)
			LD21	F1 Rat, Crl:Cd (Sd)Igs Br Vaf (♀, N=22-25)
Maternal Body Weight Change	Conley et al., 2022, 10176381	developmental (GD14-18)	GD14-18	P0 Rat, Sprague-Dawley (♀, N=4-6)
	Argus, 2000, 5080012	developmental (GD7-20)	GD7-21	P0 Rabbit, New Zealand (♀, N=17-21)
			GD21-29	P0 Rabbit, New Zealand (♀, N=12-20)
	Butenhoff et al., 2009, 757873	developmental (GD0-PND20)	GD0-20	P0 Rat, Crl:CD(SD) (♂, N=23-25)
			PND1-21	P0 Rat, Crl:CD(SD) (♀, N=23-25)
	Luebker et al., 2005, 757857	reproductive (42d prior mating-LD4)	LD1-5	P0 Rat, Crl:Cd(Sd)Igs Vaf/Plus (♀, N=6-20)
	Luebker et al., 2005, 1276160	reproductive (42d prior mating-LD20)	LD1-21	P0 Rat, Crl:Cd (Sd)Igs Br Vaf (♀, N=22-25)

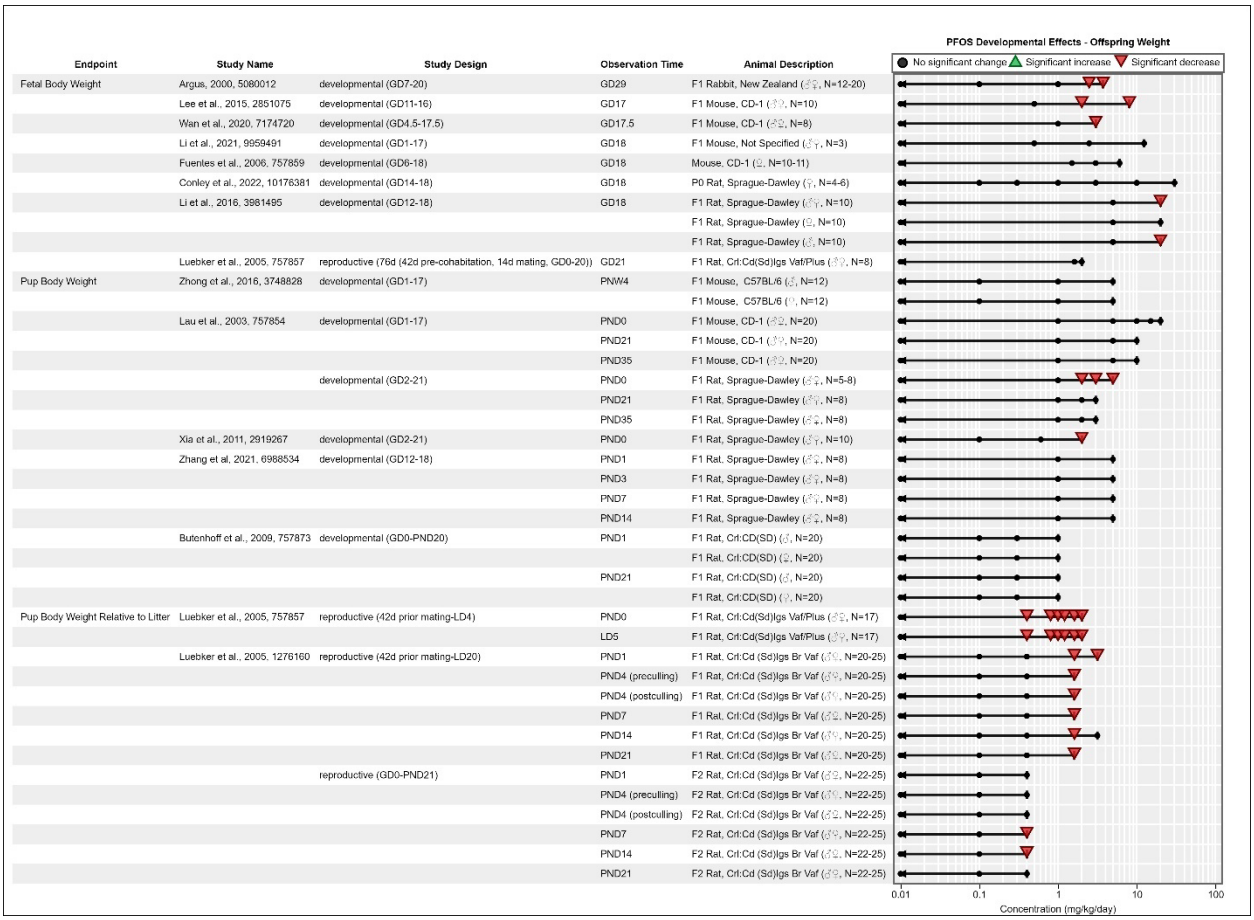


Endpoint	Study Name	Study Design	Observation Time	Animal Description
Offspring Survival	Lau et al., 2003, 757854	developmental (GD1-17)	PND0	F1 Mouse, CD-1 (♂♀, N=7)
			PND6	F1 Mouse, CD-1 (♂♀, N=7)
			PND24	F1 Mouse, CD-1 (♂♀, N=7)
	Zhang et al, 2021, 6988534	developmental (GD12-18)	PND14	F1 Rat, Sprague-Dawley (♂♀, N=93-98)
	Butenhoff et al., 2009, 757873	developmental (GD0-PND20)	PND0-4	F1 Rat, Crl:CD(SD) (♂♀, N=23-25)
			PND4-21	F1 Rat, Crl:CD(SD) (♂♀, N=23-25)
	Lau et al., 2003, 757854	developmental (GD2-21)	PND0	F1 Rat, Sprague-Dawley (♂♀, N=9)
			PND5	F1 Rat, Sprague-Dawley (♂♀, N=9)
			PND22	F1 Rat, Sprague-Dawley (♂♀, N=9)
Post-Implantation Loss	Lee et al., 2015, 2851075	developmental (GD11-16)	GD17	P0 Mouse, CD-1 (♀, N=10)
	Fuentes et al., 2006, 757859	developmental (GD6-18)	GD18	Mouse, CD-1 (♀, N=10-11)
Resorptions, Any	Argus, 2000, 5080012	developmental (GD7-20)	GD29	P0 Rabbit, New Zealand (♀, N=12-20)
Resorptions, Early	Argus, 2000, 5080012	developmental (GD7-20)	GD29	P0 Rabbit, New Zealand (♀, N=12-20)
	Fuentes et al., 2006, 757859	developmental (GD6-18)	GD18	Mouse, CD-1 (♀, N=10-11)
Resorptions, Late	Argus, 2000, 5080012	developmental (GD7-20)	GD29	P0 Rabbit, New Zealand (♀, N=12-20)
	Fuentes et al., 2006, 757859	developmental (GD6-18)	GD18	Mouse, CD-1 (♀, N=10-11)
Resorptions, Mean/Litter	Luebker et al., 2005, 757857	reproductive (76d (42d pre-cohabitation, 14d mating, GD0-20))	GD21	P0 Rat, Crl:Cd(Sd)Igs Vaf/Plus (♀, N=8)
Resorptions, Percent/Litter	Argus, 2000, 5080012	developmental (GD7-20)	GD29	P0 Rabbit, New Zealand (♀, N=12-20)
Resorptions, Total	Conley et al., 2022, 10176381	developmental (GD14-18)	GD18	P0 Rat, Sprague-Dawley (♀, N=4-6)
Stillborn Pups	Luebker et al., 2005, 1276160	reproductive (42d prior mating-LD20)	PND1	F1 Rat, Crl:Cd (Sd)Igs Br Vaf (♂♀, N=20-25)
Total Litter Resorbed	Argus, 2000, 5080012	developmental (GD7-20)	GD29	P0 Rabbit, New Zealand (♀, N=12-20)
Viability Index	Luebker et al., 2005, 1276160	reproductive (42d prior mating-LD20)	PND1-4	F1 Rat, Crl:Cd (Sd)Igs Br Vaf (♂♀, N=156-346)



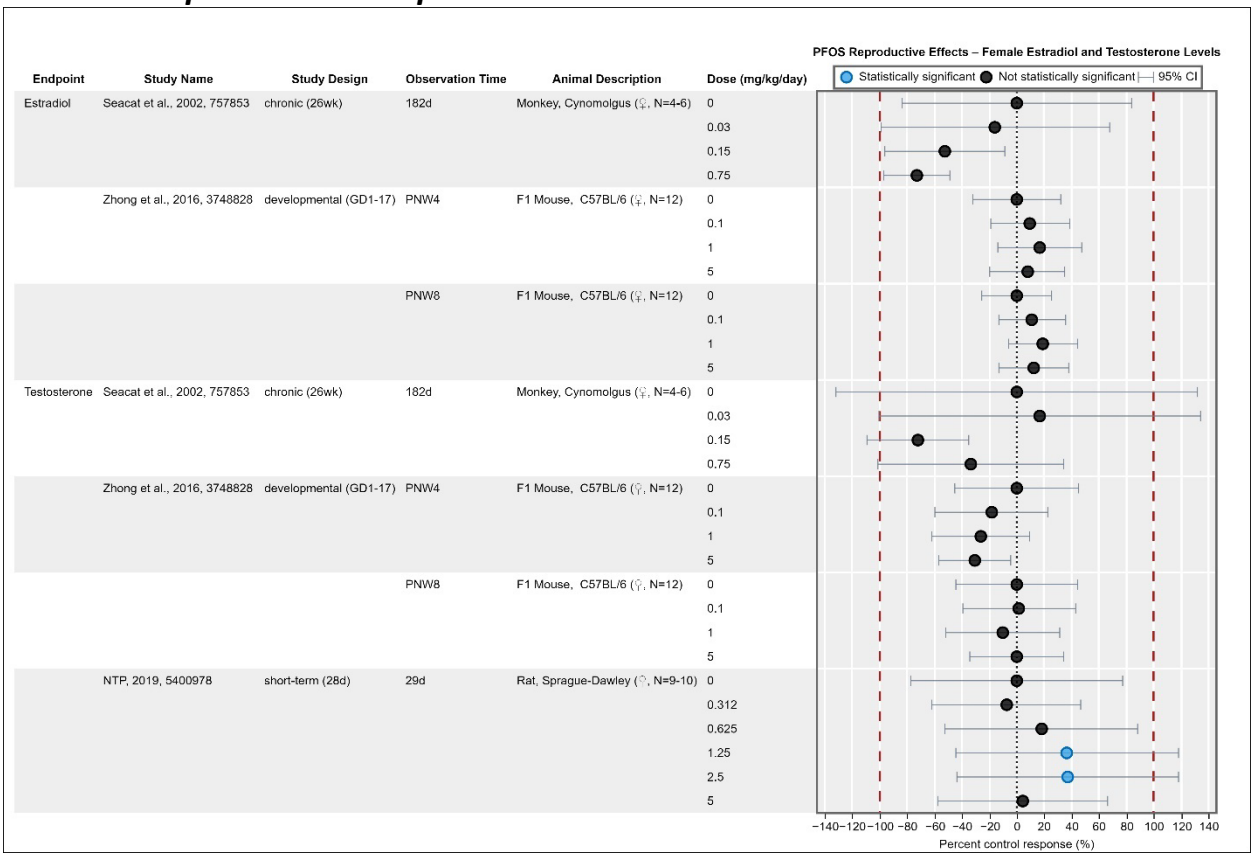


Endpoint	Study Name	Study Design	Observation Time	Animal Description
Abortions	Argus, 2000, 5080012	developmental (GD7-20)	GD29	P0 Rabbit, New Zealand (♀, N=17-21)
Dams with Stillborn Pups	Fuentes et al., 2006, 757859	developmental (GD6-18)	GD18	Mouse, CD-1 (♀, N=10-11)
	Luebker et al., 2005, 757857	reproductive (42d prior mating-LD4)	PND0	P0 Rat, Crl:Cd(Sd)Igs Vaf/Plus (♀, N=17)
	Luebker et al., 2005, 1276160	reproductive (42d prior mating-LD20)	PND1	P0 Rat, Crl:Cd (Sd)Igs Br Vaf (♀, N=20-25)
Fetuses, Dead	Argus, 2000, 5080012	developmental (GD7-20)	GD29	P0 Rabbit, New Zealand (♀, N=12-20)
	Lee et al., 2015, 2851075	developmental (GD11-16)	GD17	P0 Mouse, CD-1 (♀, N=10)
	Fuentes et al., 2006, 757859	developmental (GD6-18)	GD18	Mouse, CD-1 (♀, N=10-11)
	Luebker et al., 2005, 757857	reproductive (76d (42d pre-cohabitation, 14d mating, GD0-20))	GD21	P0 Rat, Crl:Cd(Sd)Igs Vaf/Plus (♀, N=8)
Fetuses, Dead per Litter	Fuentes et al., 2006, 757859	developmental (GD6-18)	GD18	Mouse, CD-1 (♀, N=10-11)
Fetuses, Live	Argus, 2000, 5080012	developmental (GD7-20)	GD29	P0 Rabbit, New Zealand (♀, N=12-20)
	Fuentes et al., 2006, 757859	developmental (GD6-18)	GD18	Mouse, CD-1 (♀, N=10-11)
Fetuses, Live (No. per Live Litter)	Conley et al., 2022, 10176381	developmental (GD14-18)	GD18	P0 Rat, Sprague-Dawley (♀, N=4-6)
Implantation	Argus, 2000, 5080012	developmental (GD7-20)	GD29	P0 Rabbit, New Zealand (♀, N=12-20)
	Luebker et al., 2005, 757857	reproductive (42d prior mating-LD4)	LD5	P0 Rat, Crl:Cd(Sd)Igs Vaf/Plus (♀, N=17)
Implantation Sites, Per Delivered Litter	Fuentes et al., 2006, 757859	developmental (GD6-18)	GD18	Mouse, CD-1 (♀, N=10-11)
Live Pups Born	Luebker et al., 2005, 757857	reproductive (42d prior mating-LD4)	PND0	P0 Rat, Crl:Cd(Sd)Igs Vaf/Plus (♀, N=17)
	Luebker et al., 2005, 1276160	reproductive (42d prior mating-LD20)	PND1	F1 Rat, Crl:Cd (Sd)Igs Br Vaf (♂♀, N=20-25)
Liveborn Pups, Mean/Litter	Zhang et al, 2021, 6988534	developmental (GD12-18)	PND1	P0 Rat, Sprague-Dawley (♀, N=8)
No. Dams with All Pups Dying, PND 1-4	Luebker et al., 2005, 1276160	reproductive (42d prior mating-LD20)	LD1-4	P0 Rat, Crl:Cd (Sd)Igs Br Vaf (♀, N=20-25)
No. Dams with All Pups Dying, PND 1-5	Luebker et al., 2005, 757857	reproductive (42d prior mating-LD4)	LD1-5	P0 Rat, Crl:Cd(Sd)Igs Vaf/Plus (♀, N=17)
Mortality	Xia et al., 2011, 2919267	developmental (GD2-21)	PND3	F1 Rat, Sprague-Dawley (♂♀, N=10)
Offspring Survival	Lau et al., 2003, 757854	developmental (GD1-17)	PND0	F1 Mouse, CD-1 (♂♀, N=7)
			PND6	F1 Mouse, CD-1 (♂♀, N=7)
			PND24	F1 Mouse, CD-1 (♂♀, N=7)
	Zhang et al, 2021, 6988534	developmental (GD12-18)	PND14	F1 Rat, Sprague-Dawley (♂♀, N=93-98)
	Butenhoff et al., 2009, 757873	developmental (GD0-PND20)	PND0-4	F1 Rat, Crl:CD(SD) (♂♀, N=23-25)
			PND4-21	F1 Rat, Crl:CD(SD) (♂♀, N=23-25)
	Lau et al., 2003, 757854	developmental (GD2-21)	PND0	F1 Rat, Sprague-Dawley (♂♀, N=9)
			PND5	F1 Rat, Sprague-Dawley (♂♀, N=9)
			PND22	F1 Rat, Sprague-Dawley (♂♀, N=9)
Post-Implantation Loss	Lee et al., 2015, 2851075	developmental (GD11-16)	GD17	P0 Mouse, CD-1 (♀, N=10)
	Fuentes et al., 2006, 757859	developmental (GD6-18)	GD18	Mouse, CD-1 (♀, N=10-11)
Resorptions, Any	Argus, 2000, 5080012	developmental (GD7-20)	GD29	P0 Rabbit, New Zealand (♀, N=12-20)
Resorptions, Early	Argus, 2000, 5080012	developmental (GD7-20)	GD29	P0 Rabbit, New Zealand (♀, N=12-20)
	Fuentes et al., 2006, 757859	developmental (GD6-18)	GD18	Mouse, CD-1 (♀, N=10-11)
Resorptions, Late	Argus, 2000, 5080012	developmental (GD7-20)	GD29	P0 Rabbit, New Zealand (♀, N=12-20)
	Fuentes et al., 2006, 757859	developmental (GD6-18)	GD18	Mouse, CD-1 (♀, N=10-11)
Resorptions, Mean/Litter	Luebker et al., 2005, 757857	reproductive (76d (42d pre-cohabitation, 14d mating, GD0-20))	GD21	P0 Rat, Crl:Cd(Sd)Igs Vaf/Plus (♀, N=8)
Resorptions, Percent/Litter	Argus, 2000, 5080012	developmental (GD7-20)	GD29	P0 Rabbit, New Zealand (♀, N=12-20)
Resorptions, Total	Conley et al., 2022, 10176381	developmental (GD14-18)	GD18	P0 Rat, Sprague-Dawley (♀, N=4-6)
Stillborn Pups	Luebker et al., 2005, 1276160	reproductive (42d prior mating-LD20)	PND1	F1 Rat, Crl:Cd (Sd)Igs Br Vaf (♂♀, N=20-25)
Total Litter Resorbed	Argus, 2000, 5080012	developmental (GD7-20)	GD29	P0 Rabbit, New Zealand (♀, N=12-20)
Viability Index	Luebker et al., 2005, 1276160	reproductive (42d prior mating-LD20)	PND1-4	F1 Rat, Crl:Cd (Sd)Igs Br Vaf (♂♀, N=156-346)

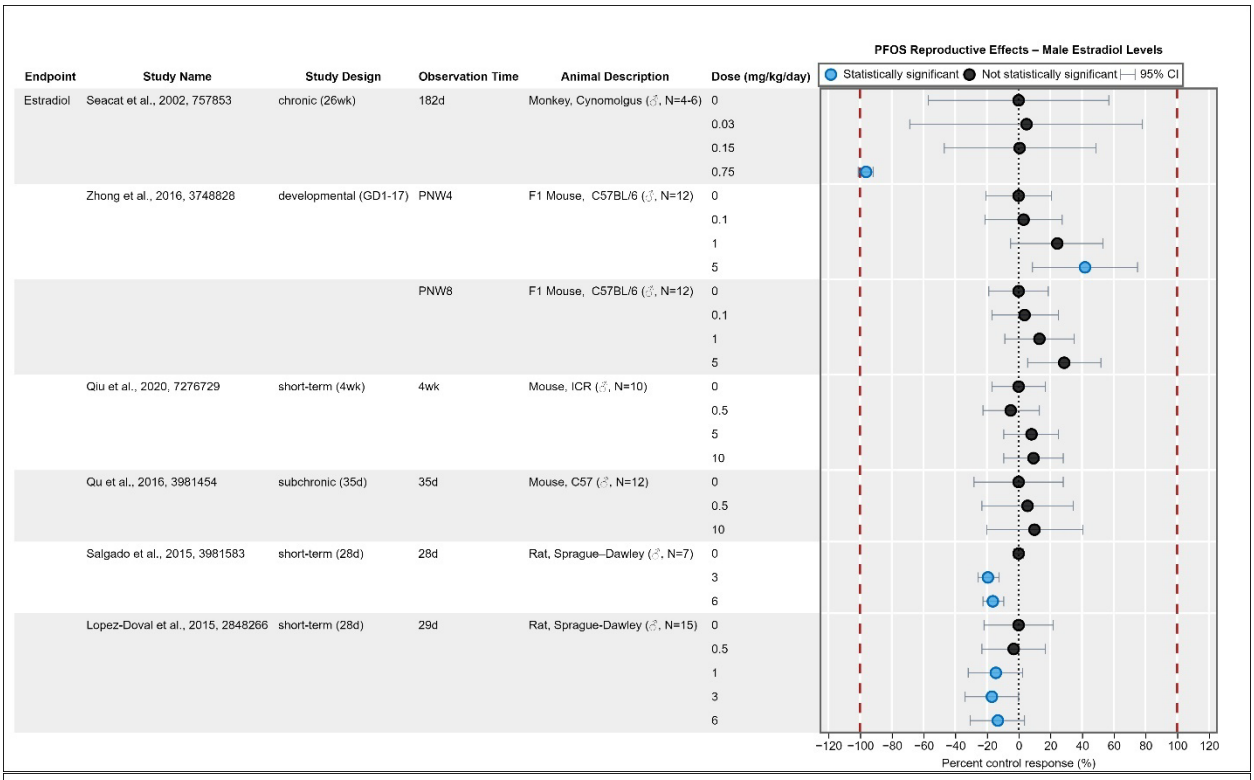


Endpoint	Study Name	Study Design	Observation Time	Animal Description
Fetal Body Weight	Argus, 2000, 5080012	developmental (GD7-20)	GD29	F1 Rabbit, New Zealand (♂♀, N=12-20)
	Lee et al., 2015, 2851075	developmental (GD11-16)	GD17	F1 Mouse, CD-1 (♂♀, N=10)
	Wan et al., 2020, 7174720	developmental (GD4.5-17.5)	GD17.5	F1 Mouse, CD-1 (♀, N=8)
	Li et al., 2021, 9959491	developmental (GD1-17)	GD18	F1 Mouse, Not Specified (♂, N=3)
	Fuentes et al., 2006, 757859	developmental (GD6-18)	GD18	Mouse, CD-1 (♀, N=10-11)
	Conley et al., 2022, 10176381	developmental (GD14-18)	GD18	P0 Rat, Sprague-Dawley (♀, N=4-6)
	Li et al., 2016, 3981495	developmental (GD12-18)	GD18	F1 Rat, Sprague-Dawley (♂, N=10)
				F1 Rat, Sprague-Dawley (♀, N=10)
				F1 Rat, Sprague-Dawley (♂, N=10)
	Luebker et al., 2005, 757857	reproductive (76d (42d pre-cohabitation, 14d mating, GD0-20))	GD21	F1 Rat, Crl:Cd(Sd)Igs Vaf/Plus (♂♀, N=8)
Pup Body Weight	Zhong et al., 2016, 3748828	developmental (GD1-17)	PNW4	F1 Mouse, C57BL/6 (♂, N=12)
				F1 Mouse, C57BL/6 (♀, N=12)
	Lau et al., 2003, 757854	developmental (GD1-17)	PND0	F1 Mouse, CD-1 (♂♀, N=20)
			PND21	F1 Mouse, CD-1 (♂♀, N=20)
			PND35	F1 Mouse, CD-1 (♂♀, N=20)
		developmental (GD2-21)	PND0	F1 Rat, Sprague-Dawley (♂♀, N=5-8)
			PND21	F1 Rat, Sprague-Dawley (♂♀, N=8)
			PND35	F1 Rat, Sprague-Dawley (♂♀, N=8)
	Xia et al., 2011, 2919267	developmental (GD2-21)	PND0	F1 Rat, Sprague-Dawley (♂♀, N=10)
	Zhang et al, 2021, 6988534	developmental (GD12-18)	PND1	F1 Rat, Sprague-Dawley (♂♀, N=8)
			PND3	F1 Rat, Sprague-Dawley (♂♀, N=8)
			PND7	F1 Rat, Sprague-Dawley (♂♀, N=8)
			PND14	F1 Rat, Sprague-Dawley (♂♀, N=8)
	Butenhoff et al., 2009, 757873	developmental (GD0-PND20)	PND1	F1 Rat, Crl:CD(SD) (♂, N=20)
				F1 Rat, Crl:CD(SD) (♀, N=20)
			PND21	F1 Rat, Crl:CD(SD) (♂, N=20)
				F1 Rat, Crl:CD(SD) (♀, N=20)
Pup Body Weight Relative to Litter	Luebker et al., 2005, 757857	reproductive (42d prior mating-LD4)	PND0	F1 Rat, Crl:Cd(Sd)Igs Vaf/Plus (♂♀, N=17)
			LD5	F1 Rat, Crl:Cd(Sd)Igs Vaf/Plus (♂♀, N=17)
	Luebker et al., 2005, 1276160	reproductive (42d prior mating-LD20)	PND1	F1 Rat, Crl:Cd (Sd)Igs Br Vaf (♂♀, N=20-25)
			PND4 (preculling)	F1 Rat, Crl:Cd (Sd)Igs Br Vaf (♂♀, N=20-25)
			PND4 (postculling)	F1 Rat, Crl:Cd (Sd)Igs Br Vaf (♂♀, N=20-25)
			PND7	F1 Rat, Crl:Cd (Sd)Igs Br Vaf (♂♀, N=20-25)
			PND14	F1 Rat, Crl:Cd (Sd)Igs Br Vaf (♂♀, N=20-25)
			PND21	F1 Rat, Crl:Cd (Sd)Igs Br Vaf (♂♀, N=20-25)
		reproductive (GD0-PND21)	PND1	F2 Rat, Crl:Cd (Sd)Igs Br Vaf (♂♀, N=22-25)
			PND4 (preculling)	F2 Rat, Crl:Cd (Sd)Igs Br Vaf (♂♀, N=22-25)
			PND4 (postculling)	F2 Rat, Crl:Cd (Sd)Igs Br Vaf (♂♀, N=22-25)
			PND7	F2 Rat, Crl:Cd (Sd)Igs Br Vaf (♂♀, N=22-25)
			PND14	F2 Rat, Crl:Cd (Sd)Igs Br Vaf (♂♀, N=22-25)
			PND21	F2 Rat, Crl:Cd (Sd)Igs Br Vaf (♂♀, N=22-25)

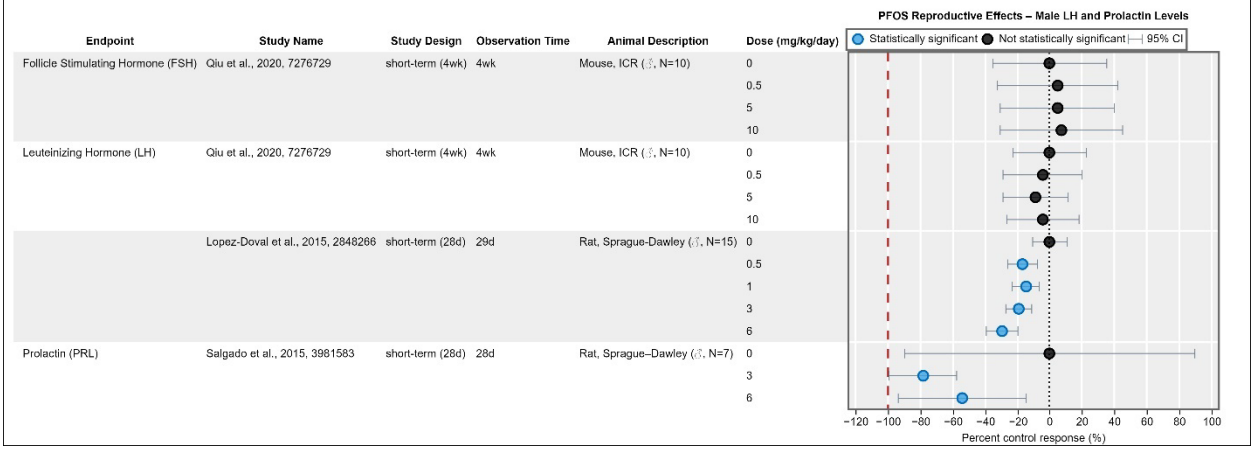
5.4 PFOS Reproductive Endpoints



Endpoint	Study Name	Study Design	Observation Time	Animal Description	Dose (mg/kg/day)
Estradiol	Seacat et al., 2002, 757853	chronic (26wk)	182d	Monkey, Cynomolgus (♀, N=4-6)	0
					0.03
					0.15
					0.75
	Zhong et al., 2016, 3748828	developmental (GD1-17)	PNW4	F1 Mouse, C57BL/6 (♀, N=12)	0
					0.1
					1
					5
			PNW8	F1 Mouse, C57BL/6 (♀, N=12)	0
					0.1
					1
					5
Testosterone	Seacat et al., 2002, 757853	chronic (26wk)	182d	Monkey, Cynomolgus (♀, N=4-6)	0
					0.03
					0.15
					0.75
	Zhong et al., 2016, 3748828	developmental (GD1-17)	PNW4	F1 Mouse, C57BL/6 (♂, N=12)	0
					0.1
					1
					5
			PNW8	F1 Mouse, C57BL/6 (♂, N=12)	0
					0.1
					1
					5
	NTP, 2019, 5400978	short-term (28d)	29d	Rat, Sprague-Dawley (♂, N=9-10)	0
					0.312
					0.625
					1.25
					2.5
					5



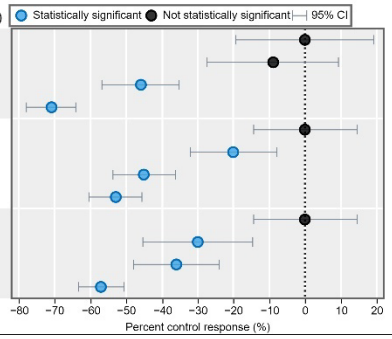
Endpoint	Study Name	Study Design	Observation Time	Animal Description	Dose (mg/kg/day)
Estradiol	Seacat et al., 2002, 757853	chronic (26wk)	182d	Monkey, Cynomolgus (♂, N=4-6)	0
					0.03
					0.15
					0.75
	Zhong et al., 2016, 3748828	developmental (GD1-17)	PNW4	F1 Mouse, C57BL/6 (♂, N=12)	0
					0.1
					1
					5
			PNW8	F1 Mouse, C57BL/6 (♂, N=12)	0
					0.1
					1
					5
	Qiu et al., 2020, 7276729	short-term (4wk)	4wk	Mouse, ICR (♂, N=10)	0
					0.5
					5
					10
	Qu et al., 2016, 3981454	subchronic (35d)	35d	Mouse, C57 (♂, N=12)	0
					0.5
					10
	Salgado et al., 2015, 3981583	short-term (28d)	28d	Rat, Sprague–Dawley (♂, N=7)	0
					3
					6
	Lopez-Doval et al., 2015, 2848266	short-term (28d)	29d	Rat, Sprague-Dawley (♂, N=15)	0
					0.5
					1
					3
					6



Endpoint	Study Name	Study Design	Observation Time	Animal Description	Dose (mg/kg/day)
Follicle Stimulating Hormone (FSH)	Qiu et al., 2020, 7276729	short-term (4wk)	4wk	Mouse, ICR (♂, N=10)	0
					0.5
					5
					10
Leuteinizing Hormone (LH)	Qiu et al., 2020, 7276729	short-term (4wk)	4wk	Mouse, ICR (♂, N=10)	0
					0.5
					5
					10
	Lopez-Doval et al., 2015, 2848266	short-term (28d)	29d	Rat, Sprague-Dawley (♂, N=15)	0
					0.5
					1
					3
					6
Prolactin (PRL)	Salgado et al., 2015, 3981583	short-term (28d)	28d	Rat, Sprague–Dawley (♂, N=7)	0
					3
					6

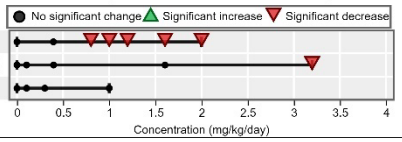
PFOS Reproductive Effects – Prolactin Family Hormone Levels in Female Mice

Endpoint	Study Name	Study Design	Observation Time	Animal Description	Dose (mg/kg/day)
Mouse placental lactogen (mPL)-II	Lee et al., 2015, 2851075	developmental (GD11-16)	GD17	P0 Mouse, CD-1 (♀, N=3)	0
					0.5
					2
					8
Mouse prolactin-like protein (mPLP)-Ca	Lee et al., 2015, 2851075	developmental (GD11-16)	GD17	P0 Mouse, CD-1 (♀, N=3)	0
					0.5
					2
					8
Mouse prolactin-like protein (mPLP)-K	Lee et al., 2015, 2851075	developmental (GD11-16)	GD17	P0 Mouse, CD-1 (♀, N=3)	0
					0.5
					2
					8



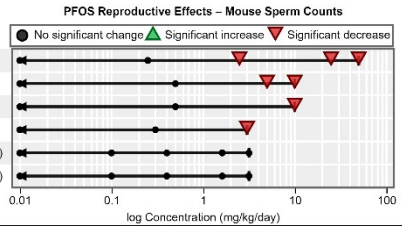
PFOS Reproductive Effects – Rat Gestation Length

Endpoint	Study Name	Study Design	Observation Time	Animal Description
Length of Gestation	Luebker et al., 2005, 757857	reproductive (42d prior mating-LD4)	GD0-21	P0 Rat, Crl:Cd(Sd)Igs Vaf/Plus (♀, N=17)
	Luebker et al., 2005, 1276160	reproductive (42d prior mating-LD20)	GD23	P0 Rat, Crl:Cd (Sd)Igs Br Vaf (♀, N=20-25)
	Butenhoff et al., 2009, 757873	developmental (GD0-PND20)	PND0	P0 Rat, Crl:CD(SD) (♀, N=23-25)

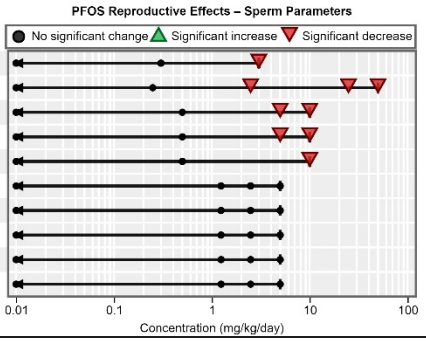


PFOS Reproductive Effects – Mouse Sperm Counts

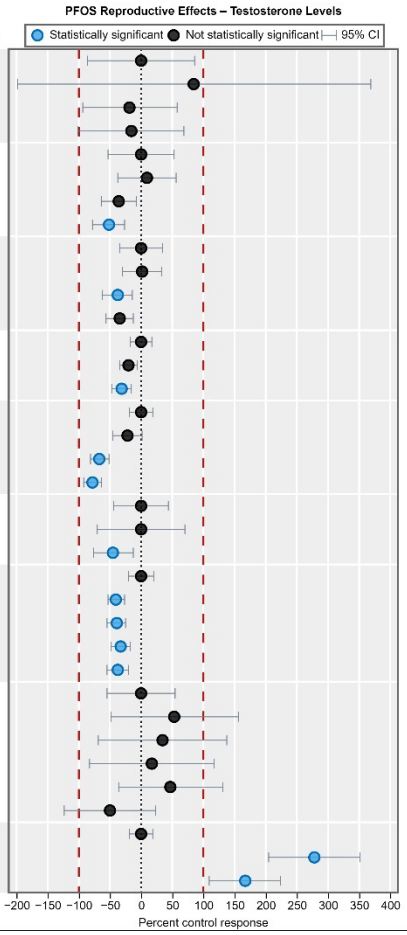
Endpoint	Study Name	Study Design	Observation Time	Animal Description
Epididymis Sperm Count	Qiu et al., 2013, 2850956	reproductive (28d)	28d	Mouse, ICR (♂, N=20)
	Qiu et al., 2016, 3981408	short-term (4wk)	4wk	Mouse, ICR (♂, N=10)
	Qu et al., 2016, 3981454	subchronic (35d)	35d	Mouse, C57 (♂, N=12)
	Lai et al., 2017, 3981773	developmental (GD1-17)	PND63	F1 Mouse, CD-1 (♂, N=5)
Fertility Index	Luebker et al., 2005, 1276160	reproductive (56d)	GD0	P0 Rat, Crl:Cd (Sd)Igs Br Vaf (♂, N=35)
		reproductive (42d prior mating-LD20)	GD0	P0 Rat, Crl:Cd (Sd)Igs Br Vaf (♀, N=35)

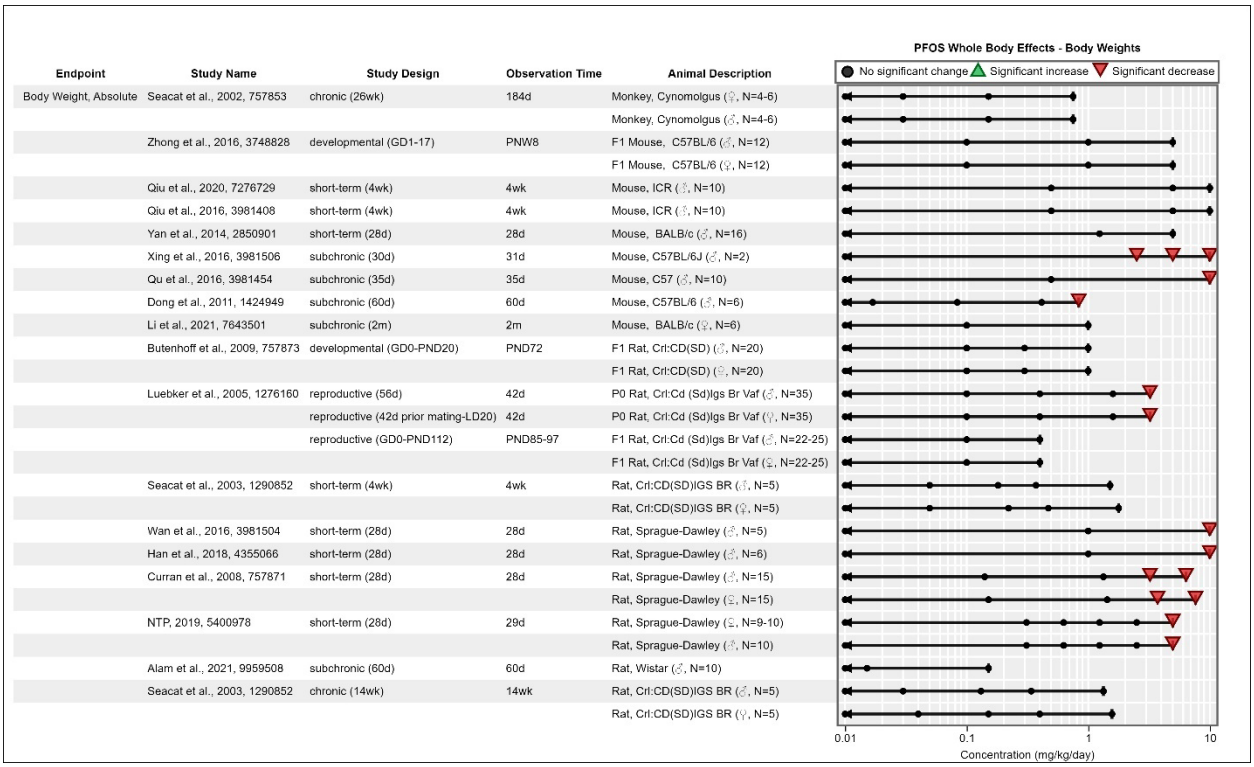


Endpoint	Study Name	Study Design	Observation Time	Animal Description
Epididymis Sperm Count	Lai et al., 2017, 3981773	developmental (GD1-17)	PND63	F1 Mouse, CD-1 (♂, N=5)
	Qiu et al., 2013, 2850956	reproductive (28d)	28d	Mouse, ICR (♂, N=20)
	Qiu et al., 2016, 3981408	short-term (4wk)	4wk	Mouse, ICR (♂, N=10)
	Qiu et al., 2020, 7276729	short-term (4wk)	4wk	Mouse, ICR (♂, N=10)
	Qu et al., 2016, 3981454	subchronic (35d)	35d	Mouse, C57 (♂, N=12)
	NTP, 2019, 5400978	short-term (28d)	29d	Rat, Sprague-Dawley (♂, N=10)
Sperm Count/g Cauda Epididymis	NTP, 2019, 5400978	short-term (28d)	29d	Rat, Sprague-Dawley (♂, N=10)
Spermatid Heads/Testis	NTP, 2019, 5400978	short-term (28d)	29d	Rat, Sprague-Dawley (♂, N=10)
Spermatid Heads/g Testis	NTP, 2019, 5400978	short-term (28d)	29d	Rat, Sprague-Dawley (♂, N=10)
Percent Motile Sperm	NTP, 2019, 5400978	short-term (28d)	29d	Rat, Sprague-Dawley (♂, N=10)



Endpoint	Study Name	Study Design	Observation Time	Animal Description	Dose (mg/kg/day)
Testosterone	Seacat et al., 2002, 757853	chronic (26wk)	182d	Monkey, Cynomolgus (♂, N=4-6)	0
					0.03
					0.15
					0.75
	Zhong et al., 2016, 3748828	developmental (GD1-17)	PNW4	F1 Mouse, C57BL/6 (♂, N=12)	0
					0.1
					1
					5
			PNW8	F1 Mouse, C57BL/6 (♂, N=12)	0
					0.1
					1
					5
	Lai et al., 2017, 3981773	developmental (GD1-17)	PND63	F1 Mouse, CD-1 (♂, N=5)	0
					0.3
					3
	Qiu et al., 2020, 7276729	short-term (4wk)	4wk	Mouse, ICR (♂, N=10)	0
					0.5
					5
					10
	Qu et al., 2016, 3981454	subchronic (35d)	35d	Mouse, C57 (♂, N=12)	0
					0.5
					10
	Lopez-Doval et al., 2015, 2848266	short-term (28d)	29d	Rat, Sprague-Dawley (♂, N=15)	0
					0.5
					1
					3
					6
	NTP, 2019, 5400978	short-term (28d)	29d	Rat, Sprague-Dawley (♂, N=9-10)	0
					0.312
					0.625
					1.25
					2.5
					5
	Alam et al., 2021, 9959508	subchronic (60d)	60d	Rat, Wistar (♂, N=10)	0
					0.015
					0.15





Endpoint	Study Name	Study Design	Observation Time	Animal Description
Body Weight, Absolute	Seacat et al., 2002, 757853	chronic (26wk)	184d	Monkey, Cynomolgus (♀, N=4-6)
				Monkey, Cynomolgus (♂, N=4-6)
	Zhong et al., 2016, 3748828	developmental (GD1-17)	PNW8	F1 Mouse, C57BL/6 (♂, N=12)
				F1 Mouse, C57BL/6 (♀, N=12)
	Qiu et al., 2020, 7276729	short-term (4wk)	4wk	Mouse, ICR (♀, N=10)
	Qiu et al., 2016, 3981408	short-term (4wk)	4wk	Mouse, ICR (♀, N=10)
	Yan et al., 2014, 2850901	short-term (28d)	28d	Mouse, BALB/c (♂, N=16)
	Xing et al., 2016, 3981506	subchronic (30d)	31d	Mouse, C57BL/6J (♂, N=2)
	Qu et al., 2016, 3981454	subchronic (35d)	35d	Mouse, C57 (♂, N=10)
	Dong et al., 2011, 1424949	subchronic (60d)	60d	Mouse, C57BL/6 (♂, N=6)
	Li et al., 2021, 7643501	subchronic (2m)	2m	Mouse, BALB/c (♀, N=6)
	Butenhoff et al., 2009, 757873	developmental (GD0-PND20)	PND72	F1 Rat, Crl:CD(SD) (♂, N=20)
				F1 Rat, Crl:CD(SD) (♀, N=20)
	Luebker et al., 2005, 1276160	reproductive (56d)	42d	P0 Rat, Crl:Cd (Sd)Igs Br Vaf (♂, N=35)
		reproductive (42d prior mating-LD20)	42d	P0 Rat, Crl:Cd (Sd)Igs Br Vaf (♀, N=35)
		reproductive (GD0-PND112)	PND85-97	F1 Rat, Crl:Cd (Sd)Igs Br Vaf (♂, N=22-25)
				F1 Rat, Crl:Cd (Sd)Igs Br Vaf (♀, N=22-25)
	Seacat et al., 2003, 1290852	short-term (4wk)	4wk	Rat, Crl:CD(SD)IGS BR (♂, N=5)
				Rat, Crl:CD(SD)IGS BR (♀, N=5)
	Wan et al., 2016, 3981504	short-term (28d)	28d	Rat, Sprague-Dawley (♂, N=5)
	Han et al., 2018, 4355066	short-term (28d)	28d	Rat, Sprague-Dawley (♂, N=6)
	Curran et al., 2008, 757871	short-term (28d)	28d	Rat, Sprague-Dawley (♂, N=15)
				Rat, Sprague-Dawley (♀, N=15)
	NTP, 2019, 5400978	short-term (28d)	29d	Rat, Sprague-Dawley (♀, N=9-10)
				Rat, Sprague-Dawley (♂, N=10)
	Alam et al., 2021, 9959508	subchronic (60d)	60d	Rat, Wistar (♂, N=10)
	Seacat et al., 2003, 1290852	chronic (14wk)	14wk	Rat, Crl:CD(SD)IGS BR (♂, N=5)
				Rat, Crl:CD(SD)IGS BR (♀, N=5)

Appendix 6 Oral Slope Factor for PFOA derived by USEPA

USEPA's cancer slope factor (CSF or SFo) for PFOA is unrealistic given the serum concentrations of PFOA in the U.S. general population as provided by the National Health and Nutrition Examination Survey (NHANES, see Appendix 4), the rates of renal and pelvis cancer in the U.S., inconsistent findings in other studies, and the known risk factors for renal cell carcinoma.

The USEPA used Shearer et al. (2021) as the basis of the PFOA CSF. This was a nested case control study within a larger trial group from 1993-2001, where the authors evaluated the concentrations of eight PFAS chemicals (including PFOA) from a single prediagnostic serum sample collected from 324 renal cell carcinoma cases and 324 individually matched controls. Due to the matched design, cases of renal cell carcinoma and controls had the same distribution for sex, race, age at enrollment, and study center. However, cases of renal cell carcinoma were more likely than controls to report being obese, have a history of hypertension at enrollment, and a diminished kidney function as assessed by estimated glomerular filtration rate (eGFR) compared with controls (although the difference in eGFR from controls was not statistically significant). The dataset used for derivation of the CSF is shown below (refer to USEPA's Human Health Toxicity Assessment for PFOA [USEPA 2024a], where ORs refers to odds ratios).

Table E-43. ORs for the Association Between PFOA Serum Concentrations and RCC in Shearer et al. (2021) and Data Used for CSF Calculations

PFOA Range (ng/mL)	x_i	OR_i	LCI_i	UCI_i	$Var(OR_i)$	w_i	$w_i x_i$	$w_i x_i^2$	$w_i x_i OR_i$	Cases	Controls
< 4	0 (reference)	1	-	-						47	81
4.0–5.5	2.75	1.47	0.77	2.80	0.234	4.267	11.734	32.267	17.248	83	79
5.5–7.3	4.4	1.24	0.64	2.41	0.176	5.685	25.012	110.053	31.015	69	83
7.3–27.2	15.25	2.63	1.33	5.20	0.837	1.195	18.224	277.909	47.928	125	81

Notes: CSF = Cancer Slope Factor; RCC = renal cell carcinoma.

The PFOA dose levels (x_i) in each quartile of exposure were calculated as the midpoint of the reported range. Because the intercept of the regression was set at 1 for a dose of 0, the midpoint of the lowest quartile was subtracted from each of the midpoint of the upper quartiles. PFOA serum concentrations in the study ranged from < 4 – 27.2 ng/mL. The CSF was calculated as the excess cancer risk associated with each ng/mL increase in serum PFOA. Note that the number of controls and cases in the lowest quartile are 81 and 47, respectively, and that only the highest quartile had a larger number of renal carcinoma cases (125) in comparison to controls (81). Shearer et al. (2021) observed statistically significant positive trends in renal cell carcinoma risk with increasing prediagnostic concentrations of PFOA (highest quartile vs lowest, odds ratio [OR] = 2.63, 95% confidence interval [CI] = 1.33 to 5.20, P trend = 0.007).

However, when adjusted for other PFAS, the trend was no longer statistically significant (P = 0.13). When PFAS concentrations were modeled continuously (per a 1-unit increase in log_2-transformed concentrations), Shearer et al. (2021) observed that a doubling in serum PFOA concentrations was associated with an approximately 70% increase in the risk of renal cell carcinoma ($OR_{continuous}$ = 1.71, 95% CI = 1.23 to 2.37, P = 0.002). The association with PFOA was similar after adjustment for other PFAS ($OR_{continuous}$ = 1.68, 95% CI = 1.07 to 2.63, P = 0.02) and remained apparent in analyses restricted to individuals without evidence of diminished kidney function and in cases diagnosed 8 or more years after phlebotomy.

There are other epidemiological studies in which renal cancer was evaluated that did not show results consistent with Shearer et al. (2021). As noted in USEPA's Human Health Toxicity Assessment (USEPA 2024a, p. 3-282) two occupational cohorts in Minnesota and West Virginia (Raleigh et al. 2014, Steenland and Woskie 2012) examined cancer mortality. Raleigh et al. (2014) reported no evidence of elevated risk for kidney cancer in 9,027 employees (with exposure to PFAS up to 3,961 ng/mL [upper confidence interval]). Note that this study used an exposure data matrix based on time weighted average air concentrations of PFOA ammonium salt and job title. However, limited biomonitoring data were available. In the West Virginia occupational cohort comprising 5,791 workers, Steenland and Woskie (2012) observed significantly elevated risk of kidney cancer deaths, but only in the highest quartile of modeled PFOA exposure (> 2,384 ng/mL-yr). The occupational studies did not show an increase in kidney cancer at the substantially lower serum concentrations observed in Shearer et al. (2021) (highest serum level was 27.2 ng/mL).

Based on the dose-response modeling performed by USEPA (2024a), the resultant CSF for PFOA is 3.52E-03 excess cancer risk per ng/mL PFOA serum concentration (refer to Table 4-12 in USEPA 2024a). As a reality check, this value can be used to calculate renal cell carcinoma risks based on serum concentrations in the US general population. Serum concentrations of PFOA are available for 1999-2000 and 2003-2018 from NHANES (see Appendix 4). PFOA was detected in approximately 98% of the US general population sampled during these timeframes. Sample collection in Shearer et al. (2021) occurred during 1993-2002. During 1999-2000 and 2003-2004 the geometric mean concentrations in the general US population were 5.22 and 3.95 ng/mL, respectively[jj]. Due to the phaseout of PFOA in the 2000's, serum concentrations of PFOA in the general population have declined. The most recently available data are from 2017 to 2018; during this timeframe the geometric mean serum concentration of PFOA in the general population was 1.42 ng/mL. Using USEPA's PFOA CSF, a serum concentration of 1.42 ng/mL would confer a cancer risk of 5.0 in 1,000 (5,000-times higher than USEPA's screening target

[jj] American Toxic Substances and Disease Registry (ATSDR). National Health and Nutrition Examination Survey (NHANES) of Perfluoroalkyl and Polyfluoroalkyl Substances: Surfactants. Available at https://www.atsdr.cdc.gov/pfas/data-research/facts-stats/ (accessed January 24, 2025). Also available in Appendix 4 of this document.

cancer risk of 1 in 1,000,000), or 0.5%. The lifetime risk for developing kidney cancer in men is about 1 in 43 (2.3%) and the lifetime risk for women is about 1 in 73 (1.4%) (American Cancer Society)[kk]. Renal cell carcinoma accounts for 90% of all cases of kidney cancer. So, the lifetime risks for developing renal cell carcinoma in men and women are 2.1% and 1.3%, respectively. Therefore, as per the USEPA's CSF for PFOA, approximately half of the newly diagnosed renal cell carcinomas in the US are due to PFOA. If one calculates the risk during the timeframe of the Shearer et al. (2021) study, where the geometric mean PFOA serum concentrations were approximately 4-5 ng/mL, the resultant risk for renal cell carcinoma would be 1.4% to 1.8%, therefore accounting for all renal cell carcinomas diagnosed during the timeframe of the study.

When one compares the PFOA CSF (29,300 $[mg/kg\text{-}d]^{-1}$) to other CSFs derived by USEPA through the Integrated Risk Information System (IRIS) program, it becomes clear that PFOA is the most potent oral carcinogen for which IRIS has ever finalized a CSF. The next most potent is for a dioxins mixture [ll], with a CSF of 6,200 $(mg/kg\text{-}d)^{-1}$. Such a determination of cancer potency is entirely unsupported by the data, because:

1) The Shearer et al. (2021) study was not appropriate for derivation of a CSF because it had: (i) a small sample size; (ii) a study design (case control) that is very weak for determining a causal relationship between serum chemical concentrations and a complicated health endpoint like cancer; and (iii) differences between the cases and controls for risk factors (e.g., obesity, hypertension) that are known to contribute to renal cell carcinoma;

2) The results are not consistent with epidemiological studies that are both better designed (cohort studies) and had higher PFOA concentrations (therefore providing better power to show an effect if there is one). Those studies either did not show a relationship between PFOA and renal cell carcinoma (Raleigh et al. 2014, Steenland and Woskie 2012), or they only showed a correlation with the highest serum concentrations (orders of magnitude higher than the Shearer et al. (2021) study); and

3) The resultant CSF generates a gross overestimation of the increased risk of renal cell carcinoma in the US general population that would be attributed to PFOA levels in serum.

[kk] American Cancer Society https://www.cancer.org/cancer/types/kidney-cancer/about/key-statistics.html (accessed January 24, 2025)

[ll] United States Environmental Protection Agency (USEPA).1987. Integrated Risk Information System (IRIS) Chemical Assessment Summary for Hexachlorodibenzo-p-dioxin (HxCDD), mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD; CASRN 57653-85-7 and 19408-74-3. US Environmental Protection Agency. Washington D.C. URL: https://iris.epa.gov/static/pdfs/0166_summary.pdf

The medical community acknowledges several risk factors for renal cell carcinoma, some of which were considered in the Shearer et al. (2021). Risk factors for renal cell carcinoma include smoking, obesity, hypertension, kidney disease, workplace exposures to certain metals or solvents (e.g., cadmium, trichloroethylene), sex (higher in males than females), race/ethnicity (highest in American Indian and Alaska Native people; higher in African Americans than in whites), long-term use of certain analgesics (acetaminophen), and several genetic and hereditary risk factors (Rose and Kim 2024, Gray and Harris 2019). In the Shearer et al. (2021) trial, cases of renal cell carcinoma were more likely than controls to report being obese, have a history of hypertension at enrollment, and a diminished kidney function as assessed by eGFR compared with controls (although the difference in eGFR from controls was not statistically significant). Risk factors not discussed or accounted for in Shearer et al. include potential workplace exposures to known human renal carcinogens, long-term use of analgesics, and genetic and hereditary risk factors. Given the known risk factors for renal cell carcinoma, which currently do not include exposure to PFOA or other PFAS compounds, the CSF derived by USEPA (2024a) does not agree with the current medical knowledge regarding renal cell carcinoma.

As discussed above, because the epidemiology studies are not appropriate for derivation of a CSF for PFOA (e.g., study limitations, inconsistent results/weight of evidence, relevant concerns discussed in Appendix 3 such as confounding by other PFAS) and the associated results (i.e., USEPA's extraordinarily high CSF) are over-predictive of cancer risk in the US based on actual NHANES serum data and cancer data, TCEQ considered the chronic carcinogenicity studies in rats as more appropriate for derivation of an oral slope factor (SFo; see Section 4.3.4).

Appendix 7 Tables of Toxicity Factors for PFOA and Associated Salts and for PFOS and Associated Salts for Input into the Texas Air Monitoring Information System (TAMIS)

Table 16. Acute Health and Welfare-Based Screening Values for Perfluorooctanoic Acid (PFOA)

Screening Level Type	Duration	Value 1 (µg/m^3)	Value 2 (ppb)	Usage	Flags	Surrogated/ RPF	Critical Effect(s)	Notes
Acute ReV	1 h	23	--	M	A	--	adverse clinical signs (wet abdomens including the perineal area, chromodacryorrhea and chromorhinorrhea, and unkempt appearance), decreased food consumption, and increased liver weight in pregnant rats	--
Acute ReV-24h	--	--	--	--	--	--	--	--
^{acute}ESL [a]	**1 h**	**6.8**	--	P	S,D	--	Same as above	--
^{acute}IOAEL	6 h	20,000	--	N	None	--	Same as above	--
^{acute}ESL$_{odor}$	--	--	--	--	--	--	--	--

Bold values used for air permit reviews

[a] Based on the acute ReV multiplied by 0.3 (i.e., HQ = 0.3) to account for cumulative and aggregate risk during the air permit review.

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 17. Acute Health and Welfare-Based Screening Values for Ammonium Perfluorooctanoate

Screening Level Type	Duration	Value 1 (µg/m^3)	Value 2 (ppb)	Usage	Flags	Surrogated/ RPF	Critical Effect(s)	Notes
Acute ReV	1 h	24	--	M	A	--	adverse clinical signs (wet abdomens including the perineal area, chromodacryorrhea and chromorhinorrhea, and unkempt appearance), decreased food consumption, and increased liver weight in pregnant rats	--
Acute ReV-24h	--	--	--	--	--	--	--	--
^{acute}ESL [a]	**1 h**	**7.1**	--	P	S,D	--	Same as above	--
^{acute}IOAEL	6 h	21,000	--	N	None	--	Same as above	--
$^{acute}ESL_{odor}$	--	--	--	--	--	--	--	--

Bold values used for air permit reviews

[a] Based on the acute ReV multiplied by 0.3 (i.e., HQ = 0.3) to account for cumulative and aggregate risk during the air permit review.

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 18. Acute Health and Welfare-Based Screening Values for Sodium Perfluorooctanoate

Screening Level Type	Duration	Value 1 (µg/m^3)	Value 2 (ppb)	Usage	Flags	Surrogated/ RPF	Critical Effect(s)	Notes
Acute ReV	1 h	24	--	M	A	--	adverse clinical signs (wet abdomens including the perineal area, chromodacryorrhea and chromorhinorrhea, and unkempt appearance), decreased food consumption, and increased liver weight in pregnant rats	--
Acute ReV-24h	--	--	--	--	--	--	--	--
^{acute}ESL [a]	**1 h**	**7.2**	--	P	S,D	--	Same as above	--
^{acute}IOAEL	6 h	21,000	--	N	None	--	Same as above	--
$^{acute}ESL_{odor}$	--	--	--	--	--	--	--	--

Bold values used for air permit reviews

[a] Based on the acute ReV multiplied by 0.3 (i.e., HQ = 0.3) to account for cumulative and aggregate risk during the air permit review.

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 19. Acute Health and Welfare-Based Screening Values for Potassium Perfluorooctanoate

Screening Level Type	Duration	Value 1 (µg/m^3)	Value 2 (ppb)	Usage	Flags	Surrogated/ RPF	Critical Effect(s)	Notes
Acute ReV	1 h	25	--	M	A	--	adverse clinical signs (wet abdomens including the perineal area, chromodacryorrhea and chromorhinorrhea, and unkempt appearance), decreased food consumption, and increased liver weight in pregnant rats	--
Acute ReV-24h	--	--	--	--	--	--	--	--
^{acute}ESL [a]	**1 h**	**7.4**	--	P	S,D	--	Same as above	--
^{acute}IOAEL	6 h	22,000	--	N	None	--	Same as above	--
$^{acute}ESL_{odor}$	--	--	--	--	--	--	--	--

Bold values used for air permit reviews

[a] Based on the acute ReV multiplied by 0.3 (i.e., HQ = 0.3) to account for cumulative and aggregate risk during the air permit review.

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 20. Chronic Health-Based Oral Toxicity Factors for PFOA

Screening Level Type	Duration	Dose (mg/kg-d)	Usage	Flags	Surrogated/ RPF	Critical Effect(s)	Notes
RfD	70 yr	2.2E-05	N	none	--	Decreased pre-weaning growth in mice	--
$^{chronic}OAEL_{(nc)}$	*In utero* and via dam's milk pre-weaning	3.1E-03	N	none	--	Same as above	--
Chronic carcinogenic dose	70 yr	1.8E-07 [a]	R	none	--	Pancreatic acinar cell adenoma and carcinoma in rats	--
$^{chronic}OAEL_{(c)}$	107 wk	1.8E-03	N	none	--	Same as above	--

[a] Based on the SFo of 55 $(mg/kg\text{-}d)^{-1}$ and a no significant risk level of 1 in 100,000 excess cancer risk.

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 21. Chronic Health-Based Oral Toxicity Factors for Ammonium Perfluorooctanoate

Screening Level Type	Duration	Dose (mg/kg-d)	Usage	Flags	Surrogated/ RPF	Critical Effect(s)	Notes
RfD	70 yr	2.3E-05	N	none	--	Decreased pre-weaning growth in mice	--
$^{chronic}OAEL_{(nc)}$	*In utero* and via dam's milk pre-weaning	3.2E-03	N	none	--	Same as above	--
Chronic carcinogenic dose	70 yr	1.9E-07 [a]	R	none	--	Pancreatic acinar cell adenoma and carcinoma in rats	--
$^{chronic}OAEL_{(c)}$	107 wk	1.9E-03	N	none	--	Same as above	--

[a] Based on the SFo of 53 $(mg/kg\text{-}d)^{-1}$ and a no significant risk level of 1 in 100,000 excess cancer risk.

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 22. Chronic Health-Based Oral Toxicity Factors for Sodium Perfluorooctanoate

Screening Level Type	Duration	Dose (mg/kg-d)	Usage	Flags	Surrogated/ RPF	Critical Effect(s)	Notes
RfD	70 yr	2.3E-05	N	none	--	Decreased pre-weaning growth in mice	--
$^{chronic}OAEL_{(nc)}$	*In utero* and via dam's milk pre-weaning	3.2E-03	N	none	--	Same as above	--
Chronic carcinogenic dose	70 yr	1.9E-07 [a]	R	none	--	Pancreatic acinar cell adenoma and carcinoma in rats	--
$^{chronic}OAEL_{(c)}$	107 wk	1.9E-03	N	none	--	Same as above	--

[a] Based on the SFo of 53 $(mg/kg\text{-}d)^{-1}$ and a no significant risk level of 1 in 100,000 excess cancer risk.

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 23. Chronic Health-Based Oral Toxicity Factors for Potassium Perfluorooctanoate

Screening Level Type	Duration	Dose (mg/kg-d)	Usage	Flags	Surrogated/ RPF	Critical Effect(s)	Notes
RfD	70 yr	2.4E-05	N	none	--	Decreased pre-weaning growth in mice	--
$^{chronic}OAEL_{(nc)}$	*In utero* and via dam's milk pre-weaning	3.3E-03	N	none	--	Same as above	--
Chronic carcinogenic dose	70 yr	2.0E-07 [a]	R	none	--	Pancreatic acinar cell adenoma and carcinoma in rats	--
$^{chronic}OAEL_{(c)}$	107 wk	2.0E-03	N	none	--	Same as above	--

[a] Based on the SFo of 51 $(mg/kg\text{-}d)^{-1}$ and a no significant risk level of 1 in 100,000 excess cancer risk.

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 24. Chronic Health-Based Oral Toxicity Factors for PFOS

Screening Level Type	Duration	Dose (mg/kg-d)	Usage	Flags	Surrogated/ RPF	Critical Effect(s)	Notes
RfD	70 yr	2.9E-05	R	None	--	Decreased neonatal weight and weight gain in rats	--
$^{chronic}OAEL_{(nc)}$	*In utero* and via dam's milk pre-weaning	1.8E-03	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 25. Chronic Health-Based Oral Toxicity Factors for Ammonium Perfluorooctanesulfonate

Screening Level Type	Duration	Dose (mg/kg-d)	Usage	Flags	Surrogated/ RPF	Critical Effect(s)	Notes
RfD	70 yr	3.0E-05	R	None	--	Decreased neonatal weight and weight gain in rats	--
$^{chronic}OAEL_{(nc)}$	*In utero* and via dam's milk pre-weaning	1.9E-03	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 26. Chronic Health-Based Oral Toxicity Factors for Sodium Perfluorooctanesulfonate

Screening Level Type	Duration	Dose (mg/kg-d)	Usage	Flags	Surrogated/ RPF	Critical Effect(s)	Notes
RfD	70 yr	3.0E-05	R	None	--	Decreased neonatal weight and weight gain in rats	--
$^{chronic}OAEL_{(nc)}$	*In utero* and via dam's milk pre-weaning	1.9E-03	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 27. Chronic Health-Based Oral Toxicity Factors for Potassium Perfluorooctanesulfonate

Screening Level Type	Duration	Dose (mg/kg-d)	Usage	Flags	Surrogated/ RPF	Critical Effect(s)	Notes
RfD	70 yr	3.2E-05	R	None	--	Decreased neonatal weight and weight gain in rats	--
$^{chronic}OAEL_{(nc)}$	*In utero* and via dam's milk pre-weaning	2.0E-03	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