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Drinking Water Health Advisory for Perfluorooctane Sulfonate (PFOS)

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Office of Children's Health Protection
Office of General Counsel
Office of Land and Emergency Management
Office of Policy
Office of Research and Development
Office of Water

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ABBREVIATIONS AND ACRONYMS

α	alpha
AFFF	aqueous film forming foams
ALT	alanine transaminase
ASBT	apical sodium dependent bile acid transporter
AUC	area under the curve
β	beta
BAF	bioaccumulation factor
BCF	bioconcentration factor
BMF	biomagnification factor
BUN	blood urea nitrogen
bw	body weight
°C	Celsius
CASRN	Chemical Abstracts Service Registry Number
CCL	Contaminant Candidate List
CDC	Centers for Disease Control and Prevention
CDR	chemical data reporting
CI	confidence interval
CL	clearance
CWA	Clean Water Act
dL	deciliter
DL	detection limit
DNT	developmental neurotoxicity
DWEL	drinking water equivalent level
DWI	drinking water intake
ECF	electro-chemical fluorination
EPA	U.S. Environmental Protection Agency
EWG	Environmental Working Group
FDA	Food and Drug Administration
FR	fecundability ratios
g	gram
GAC	granular activated carbon
GJIC	gap junctional intercellular communication
HA	Health Advisory
HDL	high density lipoprotein
HED	human equivalent dose
HESD	Health Effects Support Document
Hg	mercury
IRIS	Integrated Risk Information System
kg	kilogram
km	kilometer
K_{oc}	organic carbon-water partitioning coefficient
K_{ow}	octanol-water partition coefficient
KO	knockout
L	liter
LC/MS/MS	liquid chromatography/tandem mass spectrometry

LDL	low density lipoprotein
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOQ	limit of quantitation
µg	microgram
m^2	square meter
m^3	cubic meter
mg	milligram
mi	mile
mL	milliliter
mm	millimeter
MOA	mode of action
mol	mole
MRL	minimum reporting level
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NOAEL	no observed adverse effect level
NTCP	sodium taurocholate cotransporting polypeptide
OR	odds ratio
OST	organic solute transporter
PAC	powdered activated carbon
PBDE	polybrominated diphenyl ether
PFAS	perfluoroalkyl substance
PFBS	perfluorobutane sulfonate
PFCs	perfluorinated compounds
PFDA	perfluorododecanoic acid
PFHpA	perfluoroheptanoic acid
PFHsA	perfluorohexanoic acid
PFHxS	perfluorohexane sulfonic acid
PFOA	perfluorooctanoic acid
PFOS	perfluorooctane sulfonate
PFOSA	perfluorosulfonamide
PFPeA	perfluoropentanoic acid
pg	picogram
PK	pharmacokinetic
PND	postnatal day
POD	point of departure
POE	point of entry
POSF	perfluorooctanesulfonyl fluoride
POU	point of use
PPARα	peroxisome proliferator activated receptor alpha
ppb	parts per billion
ppm	parts per million
PTFE	polytetrafluoroethylene
PWS	public water systems
REACH	Registration, Evaluation, Authorization and Restriction of Chemicals

RfD	reference dose
RSC	relative source contribution
SDVB	polystyrenedivinylbenzene
SDWA	Safe Drinking Water Act
SGA	small for gestational age
SPE	solid phase extraction
T3	triiodothyronine
T4	thyroxine
$t_{1/2}$	chemical half-life
TMF	trophic magnification factor
TNSSS	Total National Sewage Sludge Survey
TPO	thyroid peroxidase
TSCA	Toxic Substances Control Act
TSH	thyroid-stimulating hormone
TTR	transthyretin
UCMR 3	third Unregulated Contaminant Monitoring Rule
UF	uncertainty factor
UF_A	interspecies uncertainty factor
UF_D	database deficiency uncertainty factor
UF_H	intraspecies uncertainty factor
UF_L	LOAEL uncertainty factor
UF_S	subchronic uncertainty factor
USGS	U.S. Geological Survey
UV	ultraviolet
Vd	volume of distribution
VLDL	very low density lipoprotein

EXECUTIVE SUMMARY

Perfluorooctane sulfonate (PFOS) is a synthetic, fully fluorinated organic acid; it is used in a variety of consumer products and is generated as a degradation product of other perfluorinated compounds. Because of strong carbon-fluorine bonds, PFOS is stable to metabolic and environmental degradation. PFOS is one of a large group of perfluoroalkyl substances (PFASs) that are used to make products more resistant to stains, grease, and water. These compounds have been widely found in consumer and industrial products, as well as in food items. In 2002 the only major U.S. manufacturer voluntarily agreed to phase out production of PFOS. Exposure to PFOS in the United States remains possible due to its legacy uses, existing and legacy uses on imported goods, degradation of precursors, and extremely high persistence in the environment and the human body. PFOS was detected in blood serum in up to 99% of the U.S. general population between 1999 and 2012; however, the levels of PFOS in blood have been decreasing since U.S. companies began to phase out production. Water resources contaminated by PFOS have been associated with releases from manufacturing sites, industrial sites, fire/crash training areas, and industrial or municipal waste sites where products are disposed of or applied.

The U.S. Environmental Protection Agency (EPA) is issuing a lifetime drinking water health advisory (HA) for PFOS of 0.07 micrograms per liter (µg/L) based on a reference dose (RfD) derived from a developmental toxicity study in rats; the critical effect was decreased pup body weight following exposure during gestation and lactation. PFOS is known to be transmitted to the fetus in cord blood and to the newborn in breast milk. This lifetime HA is based on the latest health effects information for noncancer and cancer effects for PFOS as described in EPA's 2016 *Health Effects Support Document for Perfluorooctane Sulfonate (PFOS*), which was revised following external peer review. Because the developing fetus and newborn are particularly sensitive to PFOS-induced toxicity, the RfD based on developmental effects also is protective of adverse effects in adults (e.g., liver and kidney toxicity). The lifetime HA is therefore protective of the population at large.

For PFOS, oral animal studies of short-term and subchronic duration are available in multiple species including monkeys, rats and mice. These studies report developmental effects (decreased body weight, survival, and increased serum glucose levels and insulin resistance in adult offspring), reproductive (mating behavior), liver toxicity (liver weight co-occurring with decreased cholesterol, hepatic steatosis), developmental neurotoxicity (altered spatial learning and memory), immune effects, and cancer (thyroid and liver). Overall, the toxicity studies available for PFOS demonstrate that the developing fetus is particularly sensitive to PFOS-induced toxicity. Human epidemiology data report associations between PFOS exposure and high cholesterol, thyroid disease, immune suppression, and some reproductive and developmental parameters, including reduced fertility and fecundity. Although some human studies suggest an association with bladder, colon, and prostate cancer, the literature is inconsistent and some studies are confounded by failure to control for risk factors such as smoking.

To derive candidate RfDs, EPA used a peer-reviewed pharmacokinetic model to calculate the average serum concentrations associated with candidate no observed adverse effect levels (NOAELs) and lowest observed adverse effect levels (LOAELs) from six studies for multiple effects. Consistent with EPA's guidance *A Review of the Reference Dose and Reference*

Concentration Processes (USEPA 2002), EPA applied protective uncertainty factors to address intraspecies variability and interspecies variability.

From a national perspective, the dominant source of human exposure to PFOS is expected to be from the diet; indoor dust from carpets and other sources also is an important source of exposure, especially for children. The HA was calculated using a relative source contribution (RSC) of 20%, which allows for other PFOS exposure sources (e.g., dust, diet, air) to make up 80% of the RfD.

EPA's risk assessment guidelines reflect that, as a general matter, a single exposure to a developmental toxin, at a critical time in development can produce an adverse effect (USEPA 1991). In addition, short-term exposure to PFASs can result in a body burden that persists for years and can increase with additional exposures. Thus, EPA recommends that the lifetime HA for PFOS of 0.07 μg/L apply to both short-term (i.e., weeks to months) scenarios during pregnancy and lactation, as well as to lifetime-exposure scenarios.

Adverse effects observed following exposures to perfluorooctanoic acid (PFOA) and PFOS are the same or similar and include effects in humans on serum lipids, birth weight, and serum antibodies. Some of the animal studies show common effects on the liver, neonate development, and responses to immunological challenges. Both compounds were also associated with tumors in long-term animal studies. The RfDs for both PFOA and PFOS are based on similar developmental effects and are numerically identical; when these two chemicals co-occur at the same time and location in a drinking water source, a conservative and health-protective approach that EPA recommends would be to compare the sum of the concentrations ([PFOA] + [PFOS]) to the HA (0.07 μg/L).

Under EPA's *Guidelines for Carcinogen Risk Assessment* (USEPA 2005a), there is Suggestive Evidence of Carcinogenic Potential for PFOS. Epidemiology studies did not find a direct correlation between PFOS exposure and the incidence of carcinogenicity in humans. In the only chronic oral toxicity and carcinogenicity study of PFOS in rats, liver and thyroid tumors (mostly adenomas) were identified in both the controls and exposed animals at levels that did not show a direct relationship to dose. The evidence for cancer in animals was judged to be too limited to support a quantitative cancer assessment (i.e., no dose-response).

1 INTRODUCTION AND BACKGROUND

The U.S. Environmental Protection Agency (EPA) developed the nonregulatory Health Advisory (HA) Program in 1978 to provide information for public health officials or other interested groups on pollutants associated with short-term contamination incidents or spills that can affect drinking water quality but are not regulated under the Safe Drinking Water Act (SDWA). At present, EPA lists HAs for more than 200 contaminants.[1]

HAs identify the concentration of a contaminant in drinking water at which adverse health effects are not anticipated to occur over specific exposure durations (e.g., one day, ten days, a lifetime). They serve as informal technical guidance to assist federal, state, and local officials, and managers of public or community water systems in protecting public health when emergency spills or other contamination situations occur. An HA document provides information on the environmental properties, health effects, analytical methodology, and treatment technologies for removing drinking water contaminants.

Perfluorooctane sulfonate (PFOS) is a manmade chemical in a large family of chemicals called perfluoroalkyl substances (PFASs) (Buck et al. 2011). PFOS has been used in a variety of consumer products, and continues to be used as a fire repellent in firefighting foams, and generated as a degradation product of other perfluorinated compounds. PFOS is very persistent in the environment and the human body; it has been detected in water, wildlife, and humans worldwide. This document, EPA's 2016 *Drinking Water Health Advisory for Perfluorooctane Sulfonate (PFOS),* presents a guideline concentration for PFOS in drinking water at which adverse health effects are not anticipated to occur over a human lifetime. This lifetime HA is based on the latest health effects information for noncancer and cancer effects for PFOS as described in EPA's *Health Effects Support Document for Perfluorooctane Sulfonate (PFOS)* (USEPA 2016b). The HA value is not a legally enforceable federal standard and is subject to change as new information becomes available. Currently no SDWA federal regulations or Clean Water Act (CWA) Ambient Water Quality Human Health Criteria exist for PFOS. The structure, principles, and approach of this document are consistent with EPA's *Framework for Human Health Risk Assessment to Inform Decision Making* (USEPA 2014a).

1.1 Safe Drinking Water Act

SDWA, as amended in 1996, requires EPA to publish a list of unregulated contaminants every 5 years that are not subject to any proposed or promulgated national primary drinking water regulations, are known or anticipated to occur in public water systems (PWSs), and might require regulation under SDWA. This list is known as the Contaminant Candidate List (CCL). PFOS is included on the third CCL (USEPA 2009a) and on the draft fourth CCL (USEPA 2015a).

[1] For more information see http://water.epa.gov/drink/standards/hascience.cfm.

As part of its responsibilities under SDWA, EPA is required to implement a monitoring program for unregulated contaminants. SDWA requires, among other things, that once every 5 years, EPA issue a list of no more than 30 unregulated contaminants to be monitored by PWSs. In 2012, EPA included PFOS in its third Unregulated Contaminant Monitoring Rule (UCMR 3), which required all large systems serving > 10,000 people, plus a statistically selected group of 800 small systems, to monitor for a 1-year period between 2013 and 2015. The last of the monitoring data are still being compiled, but results to-date indicate that PFOS has been measured at or above the minimum reporting limit (0.04 micrograms per liter [µg/L]) by approximately 2% of PWSs nationwide. To-date, PFOS has been measured above 0.07 µg/L by approximately 1% of PWSs. Approximately 1% of PWSs have reported data for which combined PFOA and PFOS results are above 0.07 µg/L. For the latest UCMR 3 results, please refer to https://www.epa.gov/dwucmr/occurrence-data-unregulated-contaminant-monitoring-rule#3.

SDWA requires EPA to make regulatory determinations for at least five CCL contaminants every 5 years. EPA must begin developing a national primary drinking water regulation when the Agency makes a determination to regulate based on three criteria:

- The contaminant may have an adverse effect on the health of persons.
- The contaminant is known to occur or there is substantial likelihood the contaminant will occur in public water systems with a frequency and at levels of public health concern.
- In the sole judgment of the Administrator, regulating the contaminant presents a meaningful opportunity for health risk reductions.

To make these determinations, the Agency uses data to analyze occurrence of these compounds in finished drinking water and data on health effects. If EPA determines the contaminant does not meet any one of the three statutory criteria, the Agency's determination is not to regulate. EPA continues to gather information to inform future regulatory determinations for PFOS under the SDWA.

EPA developed a *Health Effects Support Document for Perfluorooctane Sulfonate (PFOS)* and one for another PFAS, perfluorooctanoic acid (PFOA), to assist federal, state, tribal and local officials, and managers of drinking water systems in protecting public health when these chemicals are present in drinking water (USEPA 2016a, 2016b). The health effects support documents (HESDs) were peer-reviewed in 2014 and were revised as recommended by the peer reviewers with consideration of public comments and inclusion of additional studies published through December 2015. The revised HESD for PFOS (USEPA 2016b) provides an RfD and cancer assessment that serve as the basis for this HA.

The SDWA provides the authority for EPA to publish nonregulatory HAs or take other appropriate actions for contaminants not subject to any national primary drinking water regulation. EPA is providing this HA for PFOS to assist state and local officials evaluate risks from this contaminant in drinking water. The HA values consider variability in human response across all life stages and population groups while making allowance for contributions from other exposure media.

1.2 Current Advisories and Guidelines

Currently there are no federal regulations under the SDWA or national recommended ambient water quality criteria under the CWA for PFOS. In January 2009, EPA developed a provisional HA for PFOS in drinking water of 0.2 µg/L (USEPA 2009b). The provisional HA was developed to reflect an amount of PFOS that could cause adverse health effects in the short term (i.e., weeks to months). The provisional HA was intended as a guideline for PWSs while allowing time for EPA to develop a lifetime HA. Table 1-1 and Table 1-2 provide drinking water guideline values that were developed by states and other countries.

Table 1-1. State Guideline Values for PFOS

State	Guideline Value (µg/ L)	Source
Delaware Department of Resources and Environmental Control	0.2	DNREC (2016)
Michigan Department of Environmental Quality	0.011	Michigan DEQ (2013)
Minnesota Department of Health	0.3	MDH (2009)

Table 1-2. International Guideline Values for PFOS

Country/Agency	Guideline Value (µg/ L)		Source
	Health-based	Administrative	
German Ministry of Health	0.3	Composite precautionary guidance value for PFOA+PFOS is 0.1	German Ministry of Health (2006)
United Kingdom (UK) Drinking Water Inspectorate	1.0	Action levels: Tier 1: potential hazard Tier 2: > 0.3 Tier 3: > 1.0 Tier 4: > 9	UK Drinking Water Inspectorate (2009)
Danish Ministry of the Environment	0.1	Composite drinking water criteria are based on relative toxicity of PFOS, PFOA, and PFOSA	Danish Ministry of the Environment (2015)
Dutch National Institute for Public Health and the Environment	0.53	Negligible concentration: 0.0065	RIVM (2010)
Swedish National Food Agency	0.09	Also 0.09 for the mixture of: PFOS, PFOA, PFHxS; PFBS; PFHpA, PFHsA, PFPeA (total PFASs) 0.9: Pregnant women, women trying to get pregnant, and infants should not consume if total PFASs exceed	Livsmedelsverket (2014), cited in Danish Ministry of the Environment (2015)

Notes:
PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonate; PFBS = perfluorobutane sulfonate; PFHpA = perfluoroheptanoic acid; PFHsA = perfluorohexanoic acid; PFHxS = perfluorohexane sulfonic acid; PFOSA = perfluorosulfonamide; PFPeA = perfluoropentanoic acid

In May 2009, PFOS was listed under the United Nations Stockholm Convention on Persistent Organic Pollutants, and is subject to strict restriction. PFOS also is listed as a "Substance of Very High Concern" by the European Chemicals Agency, and is subject to restriction under Annex XVII, entry 53, of REACH (Registration, Evaluation, Authorization and Restriction of Chemicals), a European Union regulation. Several international agencies have established guideline values for PFOS (see Table 1-2).

1.3 Uses of PFOS

Perfluorinated substances, such as PFOS, are water- and lipid-resistant due to their chemical properties. Therefore, they are commonly used as surface-active agents that alter the surface tension of a mixture. Historically, PFOS was used in the United States in carpets, leathers, textiles, upholstering, paper packaging, coating additives, and as a waterproofing or stain-resistant agent. Fire resistance of aviation fluid is increased by adding PFOS to the mixture.

Most PFOS manufacturing in the United States was discontinued voluntarily by its primary manufacturer, 3M, in 2002 (USEPA 2000a). Pursuant to the Chemical Data Reporting (CDR) Rule under the Toxic Substances Control Act (TSCA), EPA gathers information on the production volumes of chemical substances in commerce, including PFOS. These figures include both domestic production and imports. Both in 1994 and 2002, reports indicated that the total production volume of PFOS in the United States was between 10,000 and 500,000 pounds. Some limited uses of PFOS-related chemicals remain for which alternatives are not yet available, including use in aviation fluid, photomicrolithography, film processing, as an etchant, and for metal plating and finishing (40 CFR §721.9582). Also, PFOS is a major ingredient in aqueous film forming foams (AFFF) used to extinguish petroleum-based fires (Seow 2013). No data for PFOS were reported under CDR since 2002 because of the PFOS phase-out and because it is likely that the quantities of PFOS imported or domestically manufactured for the limited remaining uses were less than the CDR reporting thresholds. Efforts are ongoing to develop replacement products. PFOS and related compounds continue to be produced in other countries and could enter the U.S. as imported products.

Following the voluntary phase out of PFOS by the principal worldwide manufacturer, EPA took prompt regulatory actions in 2002 and 2007 under the TSCA to require that EPA be notified before any future domestic manufacture or importation of PFOS and 270 related chemicals occurs so that EPA can determine if prohibitions or restrictions are necessary. This requirement essentially encompasses all long-chain perfluoroalkyl sulfonate chemicals on the U.S. market. More than 150 alternatives of various types have been reviewed by EPA. EPA reviews the new substances against the range of toxicity, fate, and bioaccumulation issues that have caused past concerns with perfluorinated substances, as well as any issues that could be raised by new chemistries.

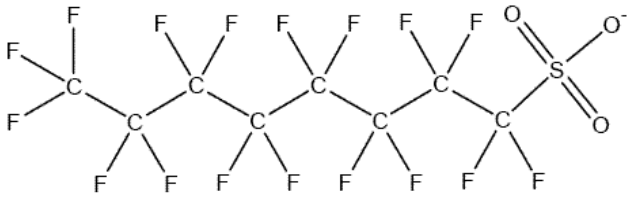
Given the limited ongoing uses of PFOS in the United States, releases to surface water and groundwater are expected to decline. Exposure to PFOS in the United States remains possible, however, because of its legacy uses, existing and legacy uses on imported goods, degradation of precursors, and the chemical's extremely high persistence in the environment.

2 NATURE OF THE STRESSOR

2.1 Physical and Chemical Properties

PFOS and its salts are fluorinated organic compounds and are part of the group of PFASs. PFOS is produced commercially from perfluorooctanesulfonyl fluoride (POSF), an intermediate used to synthesize other fluorochemicals. POSF is manufactured through a process called Simons Electro-Chemical Fluorination (ECF), in which an electric current is passed through a solution of anhydrous hydrogen fluoride and an organic feedstock of 1-octanesulfonyl fluoride, causing the carbon-hydrogen bonds on molecules to be replaced with carbon-fluorine bonds (OECD 2002). This process yields a mixture of linear and branched chain isomers (Beesoon and Martin 2015). The ECF isomer ratio is about 70% linear and 30% branched chain. Thus, all PFOS products are not structurally equivalent. PFOS also can be formed in the environment by the degradation of other POSF-derived fluorochemicals.

PFOS has an eight-carbon, fully-fluorinated backbone with an added sulfonate functional group. The chemical structure is provided in Figure 2-1.



Source: Environment Canada 2006

Figure 2-1. Chemical Structure of PFOS Anion

In the environment, the potassium salt of PFOS rapidly ionizes to PFOS. Physical and chemical properties and other reference information for PFOS are provided in Table 2-1. These properties help to define the behavior of PFOS in living systems and the environment. PFOS is a highly stable compound. It is a solid at room temperature with a low vapor pressure. Because of the surface-active properties of PFOS, it forms three layers in octanol/water, making determination of an n-octanol-water partition co-efficient (K_{ow}) difficult. No direct measurement of the pK_a of the acid has been located; however, the chemical is considered to have a low pK_a and exist as a highly dissociated anion.

PFOS is a strong acid that is generally present in solution as the perfluorooctane sulfonate anion. It is water soluble and mobile in water, with an estimated field-based log K_{oc} of 2.57. PFOS is stable in environmental media because it is resistant to environmental degradation processes, such as biodegradation, photolysis, and hydrolysis. In water, no natural degradation has been demonstrated, and dissipation is by advection, dispersion, and sorption to particulate matter. PFOS has low volatility in ionized form, but can adsorb to particles and be deposited on the ground and into water bodies. Because of its persistence, it can be transported long distances in air or water as evidenced by detections of PFOS in the Arctic media and biota, including polar bears, ocean going birds, and fish found in remote areas (Lindstrom et al. 2011a; Smithwick et al. 2006). PFOS is present in ambient air and seawater globally (Ahrens et al. 2011; Yamashita et al. 2005; Young et al. 2007).

Table 2-1. Chemical and Physical Properties of PFOS

Property	PFOS, acidic form[a]	Source
Chemical Abstracts Service Registry No. (CASRN)[b]	1763-23-1	
Chemical Abstracts Index Name	1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-1-octanesulfonic acid	
Synonyms	Perfluorooctane sulfonic acid; heptadecafluoro-1-octane sulfonic acid; PFOS acid	
Chemical Formula	$C_8HF_{17}O_3S$	
Molecular Weight (g/mol)	500.13	HSDB (2012); Lewis (2004); SRC (2016)
Color/Physical State	White powder (potassium salt)	OECD (2002)
Boiling Point	258–260 degrees Celsius (°C)	SRC (2016)
Melting Point	No data	
Vapor Pressure	$2.0X10^{-3}$ mm Hg at 25 °C (estimate)	HSDB (2012)
Henry's Law Constant	Not measureable	ATSDR (2015)
K_{ow}	Not measurable	ATSDR (2015); EFSA (2008)
K_{oc}	2.57	Higgins and Luthy (2006)
Solubility in Water	680 mg/L	OECD (2002)
Half-life in Water	Stable	UNEP (2006)
Half-life in Air	Stable	UNEP (2006)

Notes:
K_{ow} = octanol-water partition co-efficient; K_{oc} = organic carbon-water partitioning coefficient
[a] PFOS is commonly produced as a potassium salt (CASRN 2795-39-3). Properties specific to the salt are not included.
[b] The CASRN given is for linear PFOS, but the toxicity studies are based on a mixture of linear and branched; thus, the RfD applies to the total linear and branched.

2.2 Occurrence and Sources of Exposure

PFOS and other PFASs have been discharged into the environment by degradation of precursors, including perfluorosulfonamide (PFOSA) (Lindstrom et al. 2011a), and throughout the life cycle of products containing these compounds (i.e., from the point of product manufacture through its use and disposal). PFOS and other PFASs are man-made chemicals; because of their widespread use and chemical and physical properties (persistence and mobility), they have been transported into groundwater, surface waters (fresh, estuarine, and marine), and soils in the vicinity of their original source and at great distances. Point sources can result in significant exposure to people in some areas. Major sources of PFOS are described below.

2.2.1 Surface Water and Groundwater

Water resources (i.e., surface water and groundwater) are susceptible to contamination by PFOS released from industrial plants, and from the release or disposal of products containing PFOS or its derivatives. PFOS and other PFASs have been reported in wastewater and biosolids as a result of manufacturing activities, disposal of coated paper and other consumer products, and from washing of stain-repellant fabrics (Renner 2009). Historically, land application of biosolids has been a source of PFOS and other PFASs in surface water or groundwater (Lindstrom et al.

2011b; Washington et al. 2010a, 2010b). The phase-out of the use of these compounds in the United States is expected to reduce PFASs in biosolids.

Some AFFFs used to combat aviation (or other hydrocarbon) fires release PFOS to the environment (Seow 2013; USEPA 2014b). Surface and groundwater resources in close proximity to airports or other areas where these foams have been used can be contaminated (Moody et al. 2002). PFOS was reported at concentrations as high as 120 µg/L in ground water near a concrete pad formerly used for military fire-training operations in Michigan (ATSDR 2005; Moody et al. 2003). Surface water concentrations as a result of a release of approximately 22,000 L of AFFF at L.B. Pearson International Airport in Toronto, Canada, resulted in peak PFOS concentrations of 2,210 µg/L at the confluence of Etobicoke Creek and Lake Ontario (Moody et al. 2002).

PFOS is not included as an analyte in the U.S. Geological Survey (USGS) National Water Quality Assessment Program, and it is not monitored in water as part of EPA's National Aquatic Resource Surveys. PFOS has been reported in U.S. water bodies including the Tennessee River (16.8–144 nanograms per liter [ng/L]), Mississippi River (<1.0–245 ng/L), Lake Erie (11–39 ng/L), Lake Ontario (6–121 ng/L), and in the Conasuaga River (192–319 ng/L) and the Altahama River (2.6–2.7 ng/L) watersheds in Georgia (Boulanger et al. 2004; Hansen et al. 2002; Konwick et al. 2008; Nakayama et al. 2010Konwick et al. 2008). USGS collaborated with the University of Maryland and sampled three rivers and streams receiving effluent from 11 wastewater treatment facilities in the Chesapeake Bay watershed; samples were collected in July and August 2010 from the Potomac River, the Patuxent River, and Saint Mary's Run. PFOS concentrations ranged from <4.0 to 22 ng/L in the Patuxent River; from 5.4 to 8.8 ng/L in the Potomac River; and from <4.0 to 18 ng/L in Saint Mary's Run (USGS 2011). Historically, land application of sludge has also been a source of PFASs in surface water and groundwater (described in Section 2.2.7 below). The phase-out of the use of these compounds in the United States is expected to reduce PFASs in biosolids, and thus should reduce biosolids as a source of water contamination.

Studies show that PFOS occurs in marine waters. Yamashita et al. (2005) analyzed samples from the Pacific Ocean, South China Sea, and Mid-Atlantic Ocean, as well as samples from coastal waters of several Asian countries. PFOS was found at levels ranging from several thousand picograms per liter (pg/L) in water samples collected from coastal areas in Japan to tens of pg/L in the central Pacific Ocean. Yamashita et al. (2005) reported that PFOA was the predominant PFAS detected in oceanic waters, followed by PFOS.

2.2.2 Drinking Water

Under EPA's UCMR 3, PFOS was monitored by approximately 5,000 PWSs (all PWSs serving > 10,000 people, and a representative sample of 800 small PWSs) from 2013 through December 2015. The minimum reporting level (MRL) for PFOS in this survey was 0.04 µg/L. To-date, results for more than 36,000 samples have been reported by more than 4,800 PWSs for PFOS. The remainder of the results are expected to be reported by mid-2016. PFOS was measured at or above the MRL by approximately 2% of the PWS. PFOS was reported above 0.07 µg/L by approximately 1% of PWSs that have reported results. Approximately 1% of PWSs have reported data for which combined PFOA and PFOS results are above 0.07 µg/L.

The Environmental Working Group's (EWG)[2] *National Drinking Water Database* includes data on PFOS occurrence at one system between 2004 and 2009 (EWG 2015). EWG obtained their data primarily from state drinking water offices; the database includes data from 47,677 water systems in 45 states and the District of Columbia. The database showed that 24 systems reported analyzing for PFOS; of these, a single system in Minnesota reported finding detectable levels. The system had an average concentration of 0.15 µg/L and a maximum reported concentration of 0.48 µg/L. (Note that this same Minnesota system is included in UCMR 3; as of October 2015, six of twelve samples had PFOS detections with concentrations ranging from 0.046 to 0.44 µg/L).

PFOS detections in source water and drinking water were reported in several published studies. These studies frequently reported on targeted local sampling; their findings are not necessarily representative of national occurrence. For example, in New Jersey, PFOA was the most frequently detected PFAS, followed by PFOS. Monitoring of raw and finished water used as drinking water sources in 23 PWSs in New Jersey identified PFOS concentrations ranging from 0.0042 to 0.019 µg/L. PFOS was reported in both surface water and ground water from wells in unconfined or semi-confined aquifers (NJDEP 2007). A study in Minnesota reported PFOS concentrations up to 1.41 µg/L in municipal, noncommunity, and private wells monitored between 2004 and 2008 (Goeden and Kelly 2006). In Tucson, Arizona, PFOS was detected at four groundwater wells used for drinking water in 2009, with concentrations ranging from 3.9 to 65 ng/L. The wells were resampled in 2010 and three of the four wells were found to have PFOS at concentrations ≥200 ng/L (Quanrud et al. 2010).

2.2.3 Food

Because of its previous wide-use in food packaging and consumer products, PFOS ingestion from food is an important exposure source. PFOS was detected in a variety of food sources and processed food products ranging from snack foods, vegetables, meat, and dairy products to human breast milk and fish (Van Asselt et al. 2011). In a survey that included multiple food types, PFOS was the most frequently detected PFAS and was present at higher concentrations than other related compounds (Hlouskova et al. 2013). In a 2011 assessment of exposure to Americans, Egeghy and Lorber (2011) used pharmacokinetic modeling coupled with data from the Centers for Disease Control and Prevention's (CDC's) National Health and Nutrition Examination Survey (NHANES) to assess exposure to Americans from multiple routes. They concluded that food ingestion appears to be the primary route of exposure for PFOS in the general population, under typical exposure conditions. For children under typical conditions, exposure to PFOS in dust is equivalent to exposure from food. Recent evidence shows that PFOS levels in food have been declining (Johansson et al. 2014).

Schecter et al. (2010) collected 10 samples of 31 commonly consumed foods from five grocery stores in Dallas, Texas, in 2008 and analyzed them for PFOS. Equal weights of each sample were combined and composited for analysis. Dietary intakes were estimated using data from the 2007 U.S. Department of Agriculture food availability data set. For concentrations

[2] For more information see http://www.ewg.org.

below the limit of detection, a value of zero was assigned. PFOS was not detected at concentrations above the method detection limit in the foods (Schecter et al. 2010).

Tittlemier et al. (2007) conducted a Canadian total diet study that collected and analyzed 54 composite food samples. Samples were collected from 1992 to 2004, and represented fish and seafood, meat, poultry, frozen entrées, fast food, and microwave popcorn. PFASs were detected in nine composites (four meat, three fish and shellfish, one fast food, and one microwave popcorn). PFOA and PFOS were most frequently found. The authors concluded that diet represented approximately 60% of total PFAS exposure. PFOS was detected in beef steak, ground beef, luncheon meats, marine fish, freshwater fish, and microwave popcorn at concentrations ranging from 0.98 to 2.7 ng/g, wet weight. The average daily PFOS exposure was estimated at 110 ng.

Several studies are available from countries in Western Europe with diets that are comparable to the United States. Fromme et al. (2007) collected duplicate diets for 15 male and 16 female healthy subjects (16 to 45 years old) in Germany. The median daily dietary intake for PFOS was 1.4 ng/kg with a 90th percentile intake of 3.8 ng/kg. In a later study, Haug et al. (2010) estimated exposures in a Norway market basket comprised of 21 foods, three drinking water samples, one milk sample, and one tea sample. Total PFOS intake was estimated as 18 ng/day (0.26 ng/kg) for a 70 kg adult in the general population. The highest levels were found in eggs (0.66 ng/day), root vegetables/potatoes (0.13 ng/day), coffee, tea, and cocoa (0.1 ng/day), tap water (0.08 ng/day), and fats (0.08 ng/day). PFOS and PFOA together contributed about 50% of the total dietary PFAS intake. Noorlander et al. (2011) estimated mean long-term daily intakes of 0.3 ng/kg in the Netherlands using a pooled composite purchased from retail grocery chains with nationwide coverage; the 99th percentile value was 0.6 ng/kg. Important PFOS sources included milk, beef, and lean fish. In the European Union, fish seems to be an important source of human exposure to PFOS, although the data might be influenced by results of studies which collected fish from relatively polluted areas; this is likely to overestimate exposure from commonly consumed fish. It is not clear if the source of PFOS was from packaging materials, cookware, or the fish itself (EFSA 2008).

Human studies have shown that PFOA is transferred from mother to infant via cord blood and breast milk. A recent study showed that breast milk contributed > 94% of the PFOS exposure in 6-month-old infants (Haug et al. 2011). Additional information on concentrations of PFOS in breast milk is provided in section 2.4.1.

Livestock can accumulate PFOS from ingesting contaminated feed (Lupton et al. 2014) or by grazing in fields where biosolids were applied (Renner 2009; Vestergren et al. 2013). Lupton et al. (2014) exposed cattle to a single oral dose of PFOS (8 milligrams per kilogram [mg/kg]) and collected samples after 28 days. PFOS accumulated in the liver (17.0 µg/g) and muscle (1.1 µg/g), suggesting that beef consumption can be a potential dietary exposure source. When cattle were exposed to a diet of feed contaminated with 10.2 ng/kg PFOS, however, the liver (0.13 µg/kg) and muscle (0.021 µg/kg) concentrations were considerably lower (Vestergren et al. 2013) than those from the oral dosing. The Vestergren et al. (2013) study also detected PFOS in milk at a concentration of 6.2 ng/L.

Bioaccumulation in fish and other edible aquatic organisms is another route for potential dietary exposures (Bhavsar et al. 2014; Renzi et al. 2013; Stahl et al. 2014). EPA analyzed fish fillet tissue samples from U.S. rivers and from the Great Lakes as part of EPA's National Aquatic Resource Surveys. These analyses included characterizing perfluorinated compounds (PFCs) in freshwater fish on a national scale during EPA's 2008–2009 National Rivers and Streams Assessment and on a regional scale during the Great Lakes Human Health Fish Tissue Study component of the EPA 2010 National Coastal Condition Assessment. Fish were collected from randomly selected locations, including 162 urban river sites and 157 nearshore Great Lake sites, and analyzed for 13 PFASs. Results showed that 80% of urban river fish samples and 100% of Great Lakes fish samples contained some detectable PFASs. PFOS was the most frequently detected chemical (in 73% of river fish samples and 100% of Great Lakes fish samples). The statistically derived PFOS median in fillets was 10.7 ng/g for the urban river sampled population of 17,509 kilometers (km) (10,880 miles [mi]); the PFOS median in fillets was 15.2 ng/g for the Great Lakes nearshore sampled population of 11,091 km^2 (4,282 mi^2). Maximum measured PFOS concentrations were 127 ng/g and 80 ng/g in urban river fish samples and Great Lakes fish samples, respectively. Cooking of fish does not reduce the levels of PFOS in the fish (or the consumer's dietary exposure) (Bhavsar et al. 2014).

PFOS has been detected in wild-caught and farmed fish, presumably the result of bioaccumulation and/or trophic transfer. Bhavsar et al. (2014) found that PFOS concentrations were higher in wild-caught fish than farmed fish and suggested that fish caught near contaminated sites could represent a point source for recreational and subsistence fishers. The authors found that PFOS was the dominant PFAS found in four species of sports fish collected from four rivers in Canada. The concentrations were an order of magnitude higher than those found in fish from Canadian grocery stores.

In a survey of French adult freshwater anglers, PFOS was a major contributor of total PFAS exposure from fish. When results were compared with those for the general population, PFOS levels for the general population were much lower (Denys et al. 2014). In a study of French adults who consumed large amounts of seafood (n = 993), mean lower bound exposure to PFOS was 1.53 ng/kg/day compared to a lower bound of zero in the general population (n = 1918); the mean upper bound values were 2.45 ng/kg/day and 0.66 ng/kg/day, respectively (Yamada et al. 2014). In a sub-study that was restricted to 106 pregnant women, the upper bound mean was 5.25 ng/kg/day and the 95th percentile upper bound was 6.37 ng/kg/day.

In 2008 the Minnesota Department of Health suggested limiting fish consumption to one meal of fish per week when fish contained PFOS at concentrations of greater than 40 up to 200 ng/g (wet weight), one meal of fish per month with PFOS concentrations of greater than 200 up to 800 ng/g, and no consumption of fish with PFOS concentrations greater than 800 ng/g (MDH 2008a).

PFOS can occur in plants grown in contaminated soils; however, limited information indicates that PFOS does not appear to reach the edible portion of plants. For example, PFOA was shown to have a high uptake rate in corn when grown in biosolid-amended soil, but the PFOS remained in the roots and did not accumulate in edible parts of the plant (Krippner et al. 2014). PFOS accumulation in fruit crops tended to be lower than in shoot or root crops, presumably because there are more compartments through which PFOS would have to pass to reach the edible portion of the plant (Blaine et al. 2014).

PFOS and PFOSA derivatives were used to confer grease resistances to food containers, bags, and wraps (Walters and Santillo 2006). Kotthoff et al. (2015) evaluated the levels of PFOS present in baking and sandwich papers and paper baking forms (e.g., muffin cups) classified as food contact materials. Analytes were extracted using ion pair techniques and analyzed using high-performance liquid chromatography with tandem mass spectroscopy. PFOS was identified in 69% of the products tested; PFOSA was not detected. The highest concentration for PFOS was 0.2 μg per square meter (m^2).

2.2.4 Ambient Air

A number of PFASs are precursors to PFOS; they form PFOS via biotic or abiotic degradation. Some of these precursors are volatile and contribute to the formation of airborne PFOS (UNEP 2006; Vierke et al. 2011). Shoeib et al. (2011) found PFOA in all indoor air samples; PFOS was not detected. Fraser et al. (2013) also found that PFOA in serum was significantly correlated with air levels collected in offices, whereas PFOS was not. Langer et al. (2010) reported detections of PFOS, PFOA, and precursors in indoor air samples from home residences and at stores that sold outdoor equipment, furniture, and carpet.

PFOS can be transported long distances via the atmosphere and has been detected at low concentrations in areas as remote as the Arctic (Shoeib et al. 2006). PFOS levels in outdoor air have been measured in a variety of locations, most of which are countries outside the United States. Mean air concentrations in Spain and England were 4.4 pg per cubic meter (m^3) and 2.3 pg/m^3, respectively (Beser et al. 2011; Goosey and Harrad 2012). In a study conducted in China, airborne PFOS concentrations were similar (Liu et al. 2015). Fromme et al. (2009) reported a mean ambient air gas phase PFOS concentration of 1.7 (0.9–3) pg/m^3 from eight samples collected in the summertime in Albany, New York; 0.6 (0.4–1.2) pg/m^3 was present as particulate matter.

Areas near wastewater treatment plants, waste incinerators, and landfills can be point sources for PFOS in outdoor air. Concentrations in air at wastewater treatment plants (43–171 pg/m^3) and landfills (3.9 pg/m^3) are generally higher than for ambient air in cities (Ahrens et al. 2011).

2.2.5 Indoor Dust

Because of its widespread use in carpets, upholstered furniture, and other textiles, PFOS has been detected in indoor dust from homes, offices, vehicles, and other indoor spaces. Although some of these uses have been phased out, exposure could continue from legacy products and imported goods. As reported by Fraser et al. (2013), particulate matter from fabrics and carpeting are believed to be the source of the PFOS-containing dusts found in homes, offices, and automobiles.

A 2013 survey (Fraser et al. 2013) detected PFOS in samples of house dust (26.9 ng/g), office dust (14.6 ng/g), and vehicles (15.8 ng/g) collected at sites by 31 participants in Boston, Massachusetts. The Wisconsin Department of Health and Human Services collected vacuum cleaner contents from 39 homes as a means of evaluating the concentration of PFOS and 15 other PFASs in dust (Knobeloch et al. 2012). The median concentration of PFOS was 47 ng/g. PFOA, PFOS and perfluorohexane sulfonate (PFHxS) accounted for about 70% of the total PFASs

present in the dust. Egeghy and Lorber (2011) assessed Americans' PFOS exposure and concluded that ingestion of household dust and food are primary routes of PFOS exposure for 2-year old children under a typical exposure scenario; however, for highly exposed children (at the 95th percentile), PFOS exposure from dust was estimated to be approximately two times that from food. For adults, food is the dominant source under a typical exposure scenario. Where water is highly contaminated, it is the most significant source of exposure to adults and children. Oral exposures exceeded dermal and inhalation contributions of PFOS for young children (2-year-olds) as diet, under both typical and high exposure conditions. The exposure to the PFOS precursor, PFOSA, was evaluated separately and was estimated in some scenarios to make a substantial contribution to total exposure, assuming precursors are fully metabolized to PFOS in the body.

A study conducted in Belgium also found that PFOS was present in home (median: 0.5 ng/g dry weight) and office dust (median: 2.9 ng/g dry weight) (D'Hollander et al. 2010). The highest indoor dust concentration (97.1 ng/g) was found in homes in Germany (Xu et al. 2013).

2.2.6 Soils

PFOS persists in soils near manufacturing facilities and disposal sites (Xiao et al. 2015), and in areas such as military bases, where AFFFs containing PFOS were heavily used (Filipovic 2015). Measured concentrations of PFOS in surface soils from eight U.S. locations ranged from 0.6 to 2.6 ng/g (Strynar et al. 2012). In other reports U.S. values ranged from 12.2 ng/g (Xiao et al. 2015) to 8,520 ng/g (Filipovic 2015). These studies focused on two sites, the first in the Minneapolis–St. Paul, Minnesota metropolitan area where PFASs were manufactured and disposed of, and the second on a former military airport in Sweden (abandoned in 1994) where firefighting foams containing PFOS had been used. In both cases, there was groundwater contamination. Xiao et al. (2015) determined that levels of PFOS in soils increased with depth, providing evidence for migration into groundwater (see also section 2.2.1). The authors determined that no significant difference existed in PFOS levels measured in groundwater before and after the 3M phase-out, demonstrating the persistence of PFOS in groundwater supplies.

Incidental ingestion of soils represents a potential exposure route for PFOS. Regional and geographic differences in soil characteristics can influence PFOS concentrations. Research has shown that soils with high clay and organic matter content and low pH tend to retain PFOS (Das et al. 2013). Soil contamination tends to occur at manufacturing sites of producers and users or where disposal of treated products has occurred (i.e., landfills), and potentially where biosolids containing PFASs are applied. Calculated residence time in soils suggests that persistence in the environment will extend well beyond the time that PFOS manufacturing ends (Zareitalabad et al. 2013). Contaminated soils also can be transported offsite via water and wind.

2.2.7 Biosolids

Biosolids are sometimes applied as an amendment to soils as fertilizers; in some cases, the biosolids can contain PFOS. For example, in May 2007 a Decatur, Alabama, manufacturer that used PFASs notified the Decatur Utilities Dry Creek Waste Water Treatment plant that it had unknowingly discharged large amounts of perfluorocarboxylic acid precursors (PFOA and perfluorododecanoic acid [PFDA]) to the utility (USEPA 2011a). The Decatur treatment

plant also received wastewater from several other industries in the area that manufactured or used a variety of PFAS-containing materials. The incident was reported to EPA and other government agencies because biosolids from the wastewater plant had been applied to 5,000 acres of privately owned agricultural fields for the previous 12 years (1996 to 2008).

Testing revealed that the biosolids from the Decatur plant contained PFOS, PFOA, and other PFASs. Concentrations in nine soil samples from the area ranged from 589 to 1,296 parts per billion (ppb) PFOA and 55 to 2,531 ppb PFOS. Subsequently, private wells, ponds, and other surface waters near the biosolids application sites were sampled and found to contain PFOS and PFOA, in some cases at levels greater than EPA's provisional HA values. Several additional rounds of sample collection from the impacted areas confirmed the presence of PFASs, including PFOA and PFOS in the media tested (Lindstrom et al. 2011b; USEPA 2011; Washington et al. 2010a, 2010b).

PFASs were not analyzed in the 2004 EPA Total National Sewage Sludge Survey (TNSSS), as analytical methods were not available when analytes were selected. Venkatesan and Halden (2013) re-analyzed archived samples for PFCs from the TNSSS in five composites, which represented 94 wastewater treatment facilities from 32 U.S. states and the District of Columbia in 2001. PFOS was the most abundant PFAS identified (mean 403± 127 µg/kg dry weight), followed by PFOA (mean 34 ± 22 µg/kg dry weight). Armstrong et al. (2016) collected biosolid samples every two months from a large municipal water recovery facility between 2005 and 2013. The highest mean PFOS concentration reported was 22.5 µg/kg dry weight. Yoo et al. (2009) found PFOS and PFOA in plants (i.e., fescue, barley, bluegrass, and Bermuda grass) grown in soils amended with biosolids. Concentrations of PFOS ranged from 1.2 to 20.4 µg/kg. Concentrations in biosolids are expected to decline because of the phase-out of the use of PFOS and PFOA in manufacturing and industrial processes.

2.2.8 Consumer Products

Other materials that result in potential human exposure include legacy use and imported goods or continuing uses. Some examples of these uses are listed below.

- Stain/water repellants on clothing, bedding materials, upholstered furniture, carpets, and automobile interiors (e.g., ScotchGard™); these materials can be a particularly important exposure route for infants and children because of their hand-to-mouth behaviors.
- Metal plating and finishing (continuing use)
- Aqueous film forming foams (continuing use; used for firefighting)
- Photograph development (continuing use)
- Aviation fluids (continuing use)
- Semiconductor industry
- Flame repellants
- Food containers and contact paper[3]

[3] PFOS is an impurity that can be found in some grease-proofing paper coatings (Begley et al. 2005). However, in January 2016, the Food and Drug Administration amended their food additive regulations to no longer allow for the use of perfluoroalkyl ethyl containing food-contact substances as oil and water repellants for paper and paperboard for use in contact with aqueous and fatty foods.

- Oil and mining
- Cleaning products
- Paints, varnishes, sealants
- Textiles and leather

2.3 Environmental Fate

2.3.1 Mobility

PFOS is water soluble, especially as a dissociated anion, and has been found in surface, ground, and drinking water. It has low volatility in ionized form, but can adsorb to particles in air; because of its persistence, it can be transported long distances (Lindstrom et al. 2011a). PFOS has a log K_{oc} of 2.57 and does not easily adsorb to sediments or aquifer materials; therefore, it tends to stay in the water column.

2.3.2 Persistence

PFOS is stable in the environment and resistant to hydrolysis, photolysis, volatilization, and biodegradation (see Table 2-1). The carbon fluoride bond is strong, does not react with acids and bases, and is resistant to oxidation and reduction (Fromme et al. 2009). No biodegradation or abiotic degradation processes have been found, and the only dissipation mechanisms in water are dilution, advection, and sorption. The organic portion of the molecule can be destroyed by high-temperature incineration (UNEP 2006).

2.3.3 Bioaccumulation

Several criteria can be used to assess bioaccumulation, including octanol-water partition coefficient (K_{ow}), bioconcentration factors (BCFs), bioaccumulation factors (BAFs), and biomagnification or trophic magnification factors (BMFs or TMFs, respectively) (Gobas et al. 2009). The K_{ow} and BCF metrics are typically based on partitioning of organic chemicals into octanol or lipids of biota. For PFOS, partitioning appears to be more related to protein binding properties than its lipid partitioning. Thus, the K_{ow} is not a reliable measure of bioaccumulation potential for PFOS (OECD 2002; UNEP 2006). Information from field studies, BCFs, BMFs, and TMFs provide the most conclusive evidence of accumulation of chemicals in food webs (Gobas et al. 2009), and are the more appropriate metrics for gauging the potential for accumulation of PFOS in fish, wildlife, and humans.

Because of the physical-chemical properties of PFOS, K_{ow} cannot be reliably measured (UNEP 2006). Model estimates of K_{ow} have been reported; however, verification that these chemicals are within the domain of the models is often not provided. Therefore, validity of the use of such models is questionable (OECD 2002). BCFs have been reported by Martin et al. (2003) (1,100 [carcass]; 5,400 [liver]; and 4,300 [blood] for juvenile trout]. BAFs were determined from fish livers of 23 different species in Japan, ranging from 274 to 41,600 (mean = 5,550) (Taniyasu et al. 2003). In general, these values fall below traditional criteria used to assess bioaccumulation. It is recognized, however, that BCFs determined by existing standard methods derived from lipid-partitioning are not an appropriate metric for assessing

bioconcentration of PFOS (OECD 2002). Although evidence of PFOS accumulation in many organisms has been documented, reported BAFs and BCFs for the chemical fall below traditional criteria used to assess bioaccumulation.

Field evidence of PFOS biomagnification, considered to be the preferable metric for assessing bioaccumulation potential (Gobas et al. 2009), has been documented in many organisms from many locations worldwide (UNEP 2006). Trophic magnification has also been evaluated and high concentrations of PFOS were found in the liver and blood of higher-trophic-level predators that consume fish. Biomagnification factors for PFOS are reported to range from 5 to 20 in mink (liver), bald eagle, top predator fish (lake trout), walrus, narwhal (liver), and beluga (liver) (Gewurtz et al. 2014; Kannan et al. 2005; Martin et al. 2004; Tomy et al. 2004). The weight of evidence for trophic magnification was deemed sufficient to consider PFOS to be bioaccumulative by the Stockholm Convention Persistent Organic Pollutants Review Committee (OECD 2002).

2.4 Toxicokinetics

Uptake and egress of PFOS from cells is largely regulated by transporters in cell membranes based on data collected for PFOA, a structurally similar PFAS. PFOS is absorbed from the gastrointestinal tract as indicated by the serum measurements in treated animals and distributed to the tissues based on the tissue concentrations found in the pharmacokinetic studies (Cui et al. 2009; Curran et al. 2008). The highest tissue concentrations are usually those in the liver. Post-mortem tissues samples collected from 20 adults in Spain found PFOS in liver, kidney, and lung (Pérez et al. 2013). The levels in brain and bone were low. In serum, it is electrostatically bound to albumin, occupying up to 11 sites and sometimes displacing other substances that normally would occupy a site (Weiss et al. 2009). Linear PFOS chains display stronger binding than branched chains (Beesoon and Martin 2015). Binding causes a change in the conformation of serum albumin, thereby changing its affinity for the endogenous compounds it normally transports. PFOS binds to other serum proteins, including immunoglobulins and transferrin (Kerstner-Wood et al. 2003). It is not metabolized, thus any effects observed in toxicological studies are not the effects of metabolites.

Electrostatic interactions with proteins are an important toxicokinetic feature of PFOS. Studies demonstrate binding or interactions with receptors (e.g., peroxisome proliferator-activated receptor-alpha [PPARα]), transport proteins (e.g., transthyretin [TTR]), fatty acid binding proteins, and enzymes (Luebker et al. 2002; Ren et al. 2015; S. Wang et al. 2014; Weiss et al. 2009; Wolf et al. 2008, 2012; L. Zhang et al. 2013, 2014). Saturable renal resorption of PFOS from the glomerular filtrate via transporters in the kidney tubules is believed to be a major contributor to the long half-life of this compound. No studies were identified on specific tubular transporters for PFOS but many are available for PFOA. All toxicokinetic models for PFOS and PFOA are built on the concept of saturable renal resorption first proposed by Andersen et al. (2006). Some PFOS is removed from the body with bile (Chang et al. 2012; Harada et al. 2007), a process that also is transporter-dependent. Accordingly, the levels in fecal matter represent both unabsorbed material and that discharged with bile.

During pregnancy, PFOS is transferred to the fetus (Chang et al. 2009; Luebker et al. 2005b). Lactational transfer was not measured, but was inferred based on the postnatal declines in maternal serum during lactation (Chang et al. 2009). This also occurs in humans as demonstrated in the study by Mondal et al. (2014) of breastfeeding women and their infants in Ohio and West Virginia.

The arithmetic mean half-life in humans for occupationally exposed workers (Olsen et al. 2007) was 5.4 years (95% confidence interval [CI] [3.9, 6.9]). Half-lives from animals include 120.8 days for monkeys, 33 to 35 days for male and female Sprague-Dawley rats, and 36.9 days for male and female CD-1 mice (Chang et al. 2012). The half-life differences between male and female rats observed for PFOA were not observed with PFOS. This indicates a lack of gender-related differences in renal excretion for rats, and implies that the renal excretion and/resorption transporters for PFOS differ from those for PFOA. No comprehensive studies of PFOS transporters in humans or laboratory animals were identified during this assessment. A study by Zhao et al. (2015) evaluated whether transporters involved in the enterohepatic circulation of bile acids are involved in the disposition of specific PFASs, including PFOS. Uptake of PFOS was measured using hepatocytes from both humans and rats with and without sodium. The results showed sodium-dependent uptake for PFOS. Transport of PFOS was also evaluated using stable CHO Flp-In cells. PFOS was transported by human apical sodium-dependent bile salt transporter (ASBT), but not rat ASBT. Human organic solute transporter (OST) α/β was also able to transport PFOS. The study authors concluded that the long half-life and the hepatic accumulation of PFOS in humans can possibly be attributed, at least in part, to transport by sodium taurocholate cotransporting polypeptide (NTCP) and ASBT.

2.5 Human Biomonitoring Data

The CDC's Fourth National Report on Human Exposure to Environmental Chemicals (CDC 2009) included exposure data for PFOS from 2003 to 2004 collected by NHANES. PFOS was detected in 99.9% of the general U.S. population. Since that time, the CDC has issued several updates to the tables. The most recent update was released in 2015 (CDC 2015). Taken together, the data suggest that PFOS concentrations in human serum in the U.S. declined between 1999 and 2010. Over the course of the study, the geometric mean concentration of PFOS in human serum decreased from 30.4 µg/L to 6.31 µg/L and the 95th percentile concentration decreased from 75.7 µg/L to 21.7 µg/L. During this time, there has been a major reduction in environmental emissions by the manufacturers as well as a phase-out of production of C-8 compounds in the United States. Analysis of the NHANES 2003–2004 subsample demonstrated higher levels of PFOS and PFOA in males and a slight increase in levels of PFOS with age (Calafat et al. 2007).

Evidence shows that PFOS is distributed within the body and can be transferred from pregnant women to their unborn children and offspring. PFOS is detected in both umbilical cord blood and breast milk, indicating that maternal transfer occurs (Apelberg et al. 2007; Cariou et al. 2015; Tao et al. 2008; Völkel et al. 2008; Von Ehrenstein et al. 2009). In a French study (Cariou et al. 2015), PFOS was detected in 99 of 100 cord blood samples with a mean concentration of 1.28 nanograms per milliliter (ng/mL), compared to a mean of 3.77 ng/mL for the maternal serum. In a study by T. Zhang et al. (2013) evaluating samples from 31 women in China, the mean concentration of PFOS in cord blood (3.09 nanograms per gram [ng/g]) was

21% of that in maternal serum (14.6 ng/g). Differences in the results of this study likely reflect both differences in exposure and the presence of more branched chain isomers in the PFOS products that lead to the exposures present.

Kärrman et al. (2010) identified PFOS in breast milk samples from healthy women (n = 10; females 30 to 39 years old). The levels in milk (mean = 0.12 ng/mL) were low compared to liver levels. A study of 70 human breast milk samples with patients from Germany and Hungary detected PFOS in all 70 samples at concentrations ranging from 28 to 309 ng/L (Völkel et al. 2008). Mondal et al. (2014) collected serum samples from 633 breast-feeding women and 49 of their infants in West Virginia and Ohio. They found that each month of breast feeding lowered the maternal PFOS levels in serum by 3% (95% CI [-2%, 3%]) and increased the infant serum levels by 4% (95% CI [1%, 7%]). A publication from the French total diet study (Cariou et al. 2015) also examined human breast milk as an exposure route for infants using 100 mother–infant pairs. PFOS was detected in 82% of the breast milk samples with a mean concentration of 0.040 ng/mL and a maximum concentration of 0.376 ng/mL. The regression coefficient for the association between the maternal serum concentration and the detected breast milk concentrations was 0.85 (n = 19). Concentrations were below the LOD-LOQ [limit of detection-limit of quantitation] for 31 samples.

3 PROBLEM FORMULATION

3.1 Conceptual Model

The conceptual model provides useful information to characterize and communicate the potential health risks related to PFOS exposure from drinking water. The sources of PFOS, the routes of exposure for biological receptors of concern (e.g., various human activities related to ingested tap water such as drinking, food preparation, and consumption), the potential assessment endpoints (e.g., effects such as liver toxicity and developmental effects), and adverse health effects in the populations at risk due to exposure to PFOS are depicted in the conceptual diagram below (Figure 3-1).

3.1.1 Conceptual Model Diagram for Exposure via Finished Drinking Water

The conceptual model is intended to explore potential links of exposure to a contaminant or stressor with the adverse effects and toxicological endpoints important for management goals, including the development of drinking water HA values. Boxes that are more darkly shaded indicate pathways that were considered quantitatively in estimating the advisory level, whereas the lightly shaded boxes were only considered from a qualitative perspective.

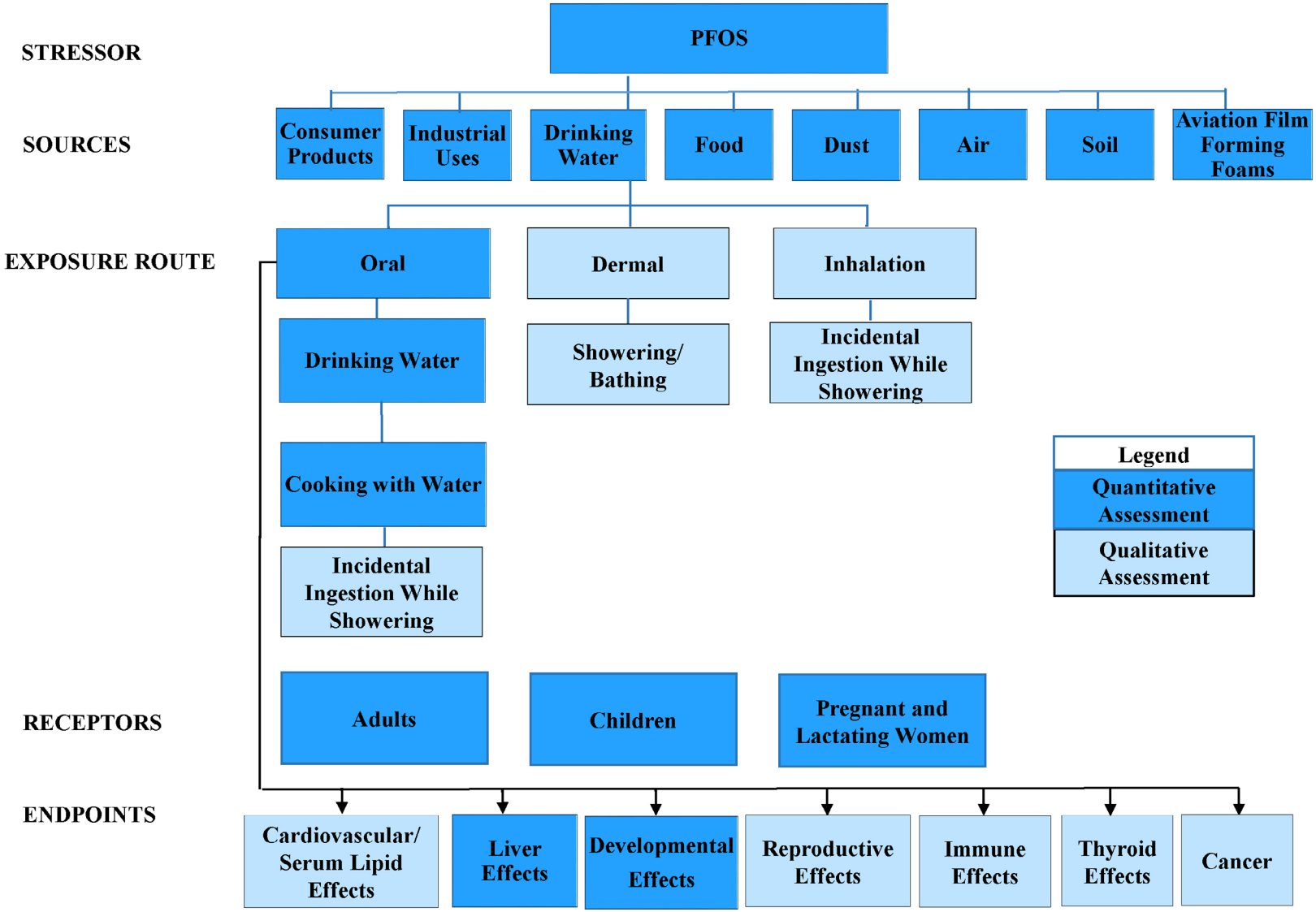


Figure 3-1. Conceptual Model for PFOS in Finished Drinking Water

3.1.2 Factors Considered in the Conceptual Model for PFOS

Stressors: For this HA, the stressor is PFOS in drinking water. The drinking water can be derived from public water facilities or private wells.

Sources: Sources of PFOS include both ground and surface waters used for drinking. Multiple potentially important sources of PFOS and precursors exist in addition to drinking water, such as foods, indoor dust in a home or work environment, indoor and outdoor air, soil, consumer products within the homes or places of work (including children's schools), and industrial products. The relative contribution of drinking water versus other sources is addressed in the Relative Source Contribution section of the document (section 3.2.5). This HA applies only to drinking water.

Routes of exposure: Exposure to PFOS from contaminated drinking water sources can occur via oral exposure (drinking water, cooking with water, and incidental ingestion from showering); dermal exposure (contact of exposed parts of the body with water containing PFOS during bathing or showering, dishwashing); and inhalation exposure (during bathing or showering or using a humidifier or vaporizer). There is limited information identifying health effects from inhalation or dermal exposures to PFOS in humans and animals. Therefore, these routes of exposure are not quantitatively used in the derivation of the HA. PFOS has a low vapor pressure and is not expected to be present in air except as bound to particulate matter and aerosols formed from devices such as shower heads and humidifiers that aerosolize tap water. Toxicity data are available for oral exposure from drinking water, but not the other exposure routes (inhalation and dermal exposures). PFOS is not removed by heating water and can increase in concentration when the water is boiled.

Receptors: The receptors are those in the general population (adults, infants and children) who could be exposed to PFOS from tap water through dermal contact and inhalation and/or ingestion at their homes, workplaces, schools, and daycare centers.

Endpoints: Epidemiology data report associations between PFOS exposure and high cholesterol and reproductive and developmental parameters. The strongest associations are related to serum lipids with increased total cholesterol and high density lipoproteins (HDLs). Data also suggest a correlation between higher PFOS levels (> 0.033 µg/mL) and decreases in female fecundity and fertility, as well as decreased body weights in offspring and other measures of postnatal growth. Several human epidemiology studies evaluated the association between PFOS and cancers including bladder, colon, and prostate (Alexander et al. 2003; Alexander and Olsen 2007; Mandel and Johnson 1995). A large increase in mortality risk from bladder cancer was demonstrated, and a subsequent study of bladder cancer incidence in the same cohort found rate ratios of 1.5 to 1.9 in the two highest cumulative exposure categories compared to an internal referent population (Alexander et al. 2003; Alexander and Olsen 2007). The risk estimates lacked precision because the number of cases were small. Smoking prevalence was higher in the bladder cancer cases, but the analysis did not control for smoking because data were missing for deceased workers; therefore, positive confounding by smoking is a possibility in this analysis. No elevated bladder cancer risk was observed in a nested case-control study in a Danish cohort with plasma PFOS concentrations at enrollment between 0.001 and 0.0131 µg/mL (Eriksen et al. 2009). Other studies that evaluated cancer risk for specific sites (e.g., prostate,

breast) in the general population were inconsistent (Bonefeld-Jørgensen et al. 2011, 2014; Hardell et al. 2014; Innes et al. 2014) (see section 4.1.2).

The associations for most epidemiology endpoints are mixed. Although mean serum values are presented in the human studies, actual estimates of PFOS exposure (i.e., doses/duration) are not currently available. Thus, the serum level at which the effects were first manifest and whether the serum had achieved steady state at the point the effect occurred cannot be determined. It is likely that some of the human exposures that contribute to serum PFOS values come from PFOS derivatives or precursors that break down metabolically to PFOS. These compounds might originate from PFOS in diet and materials used in the home, which creates potential for confounding. Additionally, most of the subjects of the epidemiology studies have many PFASs and/or other contaminants in their blood. Although the study designs adjust for other potential toxicants as confounding factors, their presence constitutes a level of uncertainty that is usually absent in the animal studies.

Taken together, the weight of evidence for human studies supports the conclusion that PFOS exposure is a human health hazard. At this time, EPA concludes that the human studies are adequate for use qualitatively in the identification hazard and are supportive of the findings in laboratory animals. EPA plans to begin another effort to determine the range of perfluoroalkyl compounds for which an Integrated Risk Information System (IRIS) assessment is needed, as indicated in the 2015 IRIS Multi Year Agenda.[4]

For PFOS, oral studies of short-term, subchronic, and chronic duration are available in multiple species including monkeys, rats, and mice (see section 4.1.1). The animal studies evaluating effects during development show low pup birth weight accompanied by increased pup mortality (at slightly higher doses) and developmental neurotoxicity. Increases in liver weight and hypertrophy accompanied by biomarkers of adversity such as necrosis, inflammation, fibrosis, and/or steatosis at one or more doses were also observed following PFOS exposures. EPA quantitatively evaluated (i.e., modeled serum concentrations) for the developmental (e.g., pup body weight, neurodevelopment, pup survival) and liver effects.

In most animal studies, changes in relative and/or absolute liver weight appears to be the most common effect observed with or without other hepatic indicators of adversity identifying increased liver weight as a common indicator of PFOS exposure. The liver also contains the highest levels of PFOS when analyzed after test animal sacrifice. The increases in liver weight and hypertrophy, however, also can be associated with activation of cellular PPARα receptors, making it difficult to determine if this change is a reflection of PPARα activation or an indication of PFOS toxicity. The PPARα response is greater in rodents than in humans. EPA evaluated liver disease and liver function resulting from PFOS exposure in studies where liver weight changes and other indicators of adversity such as necrosis, inflammation, fibrosis, and/or steatosis (fat accumulation in the liver) or increases in liver or serum enzymes indicative of liver damage are observed. Only the doses associated with the adverse effects were used for the quantification of risk. A single chronic study evaluating carcinogenicity (i.e., hepatocellular adenomas) in rats is available for PFOS (Thomford 2002).

[4] For more information on the IRIS agenda see https://www.epa.gov/iris/iris-agenda.

3.2 Analysis Plan

3.2.1 Health Advisory Guidelines

Assessment endpoints for HAs can be developed for both short-term (1-day and 10-day) and lifetime exposure periods using information on the noncarcinogenic and carcinogenic toxicological endpoints of concern. Where data are available, endpoints will reflect susceptible and/or more highly exposed populations.

- A 1-day HA is typically calculated for an infant (0 to12 months or a 10-kg child), assuming an acute exposure to the chemical; it is generally derived from a study of less than 7 days duration.
- A 10-day HA is typically calculated for an infant (0-12 months or a 10-kg child), assuming a limited period of exposure of one to two weeks; it is generally derived from a study of 7 to 30 days duration.
- A lifetime HA is derived for an adult (> 21 years old or an 80-kg adult), and assumes an exposure period over a lifetime (approximately 70 years). It is usually derived from a chronic study of 2 years duration, but subchronic studies can be used by adjusting the uncertainty factor employed in the calculation. For carcinogens, the HA documents typically provide the concentrations in drinking water associated with a range of risks (from one excess cancer case per 10,000 persons exposed to one excess cancer case per million persons exposed) for Group A and B carcinogens and those classified as known or likely carcinogens (USEPA 1986, 2005a). Cancer risks are not provided for Group C carcinogens or those classified as "suggestive," unless the cancer risk has been quantified.

3.2.2 Establishing the Data Set

The *Health Effects Support Document for Perfluorooctane Sulfonate (PFOS)* (USEPA 2016b) provides the health effects basis for development of the HA, including the science-based decisions providing the basis for estimating the point of departure (POD). To develop the HESD and HA for PFOS, EPA assembled available information on toxicokinetics, acute, short-term, subchronic, and chronic toxicity and cancer in humans and animals. For a more detailed description of the literature review search and strategy for inclusion and exclusion see the Background and Appendix A of the HESD for PFOS.

Briefly, through a literature search, literature was identified for retrieval, review, and inclusion in the document using the following criteria:

- The study examines a toxicity endpoint or population that had not been examined by studies already present in the draft assessment.
- Aspects of the study design, such as the size of the population exposed or quantification approach, make it superior to key studies already included in the draft document.
- The data contribute substantially to the weight of evidence for any of the toxicity endpoints covered by the draft document.
- Elements of the study design merit its inclusion in the draft assessment based on its contribution to the mode of action (MOA) or the quantification approach.

- The study elucidates the MOA for any toxicity endpoint or toxicokinetic property associated with PFOS exposure.
- The effects observed differ from those in other studies with comparable protocols.
- The study was relevant to drinking water exposures and to the U.S. population.

In addition, an evaluation of available data was performed by EPA to determine data acceptability. The following study quality considerations from USEPA's (2002) *A Review of the Reference Dose and Reference Concentration Processes* were used in selection of the studies for inclusion in the HESD and development of the HA.

- Clearly defines and states hypothesis.
- Adequately describes the study protocol, methods, and statistical analyses.
- Evaluates appropriate endpoints. Toxicity depends on the amount, duration, timing, and pattern of exposure, and may range from frank effects (e.g., mortality) to more subtle biochemical, physiological, pathological, or functional changes in multiple organs and tissues.
- Applies appropriate statistical procedures to determine an effect.
- Establishes dose-response relationship (i.e., no observed adverse effect level (NOAEL) and/or lowest observed adverse effect level (LOAEL) or data amenable to modeling of the dose-response to identify a POD for a change in the effect considered to be adverse [out of the range of normal biological viability]). The NOAEL is the highest exposure level at which there are no biologically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control. The LOAEL is the lowest exposure level at which there are biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control group.

The studies included in the HESD and HA were determined to provide the most current and comprehensive description of the toxicological properties of PFOS and the risk it poses to humans exposed through their drinking water.

After the available, reliable studies were evaluated for inclusion in the HESD and HA, critical studies were selected for consideration based on factors including exposure duration (comparable to the duration of the HAs being derived), route of exposure (e.g., oral exposure via drinking water, gavage, or diet), species sensitivity, comparison of the POD with other available studies demonstrating an effect, and confidence in the study (USEPA 1999). Uncertainty factors appropriate for the studies selected are then applied to the potential PODs to account for variability and uncertainty in the available data.

3.2.3 Approach for HA Calculation

For PFOS, toxicity and exposure data were used to develop a lifetime HA. EPA used measures of effect and estimates of exposure to derive the lifetime HA using the following three-step process:

Step 1: Adopt a Reference Dose (RfD) or calculate an RfD using the appropriate point of departure (POD). The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily human exposure to the human population (including sensitive subgroups)

that is likely to be without an appreciable risk of deleterious effects during a lifetime. In the case of PFOA, the POD is the human equivalent dose (HED) derived from the modeled serum concentration representing either an NOAEL or LOAEL experimental dose after applying uncertainty factors established following EPA guidelines.

$$\text{RfD} = \frac{\text{HED}_{\text{NOAEL}} \text{ or } \text{HED}_{\text{LOAEL}}}{\text{UF}}$$

Where:

HED $_{\text{NOAEL}}$ = The HED from the modeled average serum representing the highest of the given doses that lacked adverse effects (mg/kg/day).
HED $_{\text{LOAEL}}$ = The HED from the modeled average serum representing the lowest of the given doses that results in adverse effects (mg/kg/day) and of an appropriate duration and endpoint to use for a lifetime HA.
UF = Total Uncertainty Factor established in accordance with EPA guidelines considering variations in sensitivity among humans, differences between animals and humans, the duration of exposure in the key study compared to a lifetime of the species studied, whether the HED is a dose that caused an effect or no effect, and the completeness of the toxicology database.

Step 2: Calculate a Drinking Water Equivalent Level (DWEL) from the RfD. The DWEL assumes that 100% of the exposure comes from drinking water.

$$\text{DWEL} = \frac{\text{RfD x bw}}{\text{DWI}}$$

Where:

RfD = Reference dose (mg/kg bw/day)
bw = Assumed body weight (kg)
DWI = Assumed human daily drinking water intake (L/day)

Step 3: Calculation of the Lifetime HA. The lifetime HA is calculated by factoring in other sources of exposure (e.g., air, food, soil) in addition to drinking water using the methodology described for calculation of a relative source contribution (RSC) described in USEPA (2000b) and section 6.1.

$$\text{Lifetime HA} = \text{DWEL x RSC}$$

Where:

DWEL = Drinking water equivalent level calculated from step 2 (mg/L)
RSC = Relative source contribution

3.2.4 Measures of Effect

The animal toxicology studies were used in the dose-response assessment of PFOS. These studies demonstrated dose-related effects on systemic and developmental endpoints in multiple species (monkeys, rats, mice) following exposure to PFOS for durations of 19 to 182 days; these

are described in detail in the HESD for PFOS. The studies selected for pharmacokinetic analysis were chosen based on their experimental design, data quality, dose-response data identified through the range of experimental NOAELs/LOAELs, and serum measurements of PFOS.

EPA used a peer-reviewed pharmacokinetic model developed by Wambaugh et al. (2013) to calculate the average serum concentrations associated with the candidate NOAELs and LOAELs from the toxicological database. Average serum levels of PFOS from the model were used to determine the HED associated with the study NOAEL and LOAEL. The Wambaugh et al. (2013) model is based on the Andersen et al. (2006) concept that saturable renal resorption is responsible for the long serum half-lives seen in humans and animals.

A unique feature of the pharmacokinetic approach is the use of a single model for the three species and reliance on the serum PFOS level as the measure of exposure. For each species, the model accommodated the appropriate toxicokinetic variables for the species/strain. The pharmacokinetic analysis facilitated examination for consistency in the average serum values associated with effect and no-effect doses from the animal PFOS studies. A nonhierarchical model for parameter values was assumed wherein a single numeric value represented all individuals of the same species, gender, and strain. Body weight, the number of doses, and magnitude of the doses were the only parameters that varied.

3.2.5 Relative Source Contribution

The RSC is applied in the HA calculation to ensure that an individual's total exposure from a contaminant (i.e., PFOS) does not exceed the RfD. The RSC is the portion of the RfD attributed to drinking water (directly or indirectly in beverages like coffee tea or soup); the remainder of the RfD is allocated to other potential sources. In the case of PFOS, other potential sources include ambient air, foods, bottled water, incidental soil/dust ingestion, consumer products and others (see sections 2.2 and 6.1). The RSC for the HA is based on exposure to the general population.

EPA derived an RSC for PFOS by using the Exposure Decision Tree approach (USEPA 2000b) (see section 6.1). To use that approach, EPA compiled information for PFOS on its uses, chemical and physical properties, occurrences in other potential sources (e.g., air, food), and releases to the environment. To determine the RSC to be used in the HA calculation for PFOS, EPA then used the information to address the questions posed in the Exposure Decision Tree. Some of the important items evaluated in the Exposure Decision Tree are:

- The adequacy of data available for each relevant exposure source and pathway.
- The availability of information sufficient to characterize the likelihood of exposure to relevant sources.
- Whether there are significant known or potential uses/sources other than the source of concern (i.e., ambient water and fish/seafood from those waters).
- Whether information on each source is available to characterize exposure.

In cases where environmental and/or exposure data are lacking, the Exposure Decision Tree approach results in a recommended RSC of 20%. This 20% RSC value may be replaced where sufficient data are available to develop a scientifically defensible alternative value. When appropriate, if scientific data demonstrating that sources and routes of exposure other than

drinking water are not anticipated for the pollutant in question, the RSC may be raised to 80% based on the available data (USEPA 2000b).

4 EFFECTS ASSESSMENT

The database for PFOS includes a large number of laboratory animal toxicity studies, as well as numerous epidemiology studies. These animal and human studies are described below and in greater detail in the HESD for PFOS. Because of uncertainties associated with the human data (described above), EPA is relying on animal data to quantitatively assess effects; however, the epidemiology studies provide important data to establish probable links between PFOS exposure to humans and health effects. In particular, effects on the liver enzymes indicative of liver effects, low birth weight, antibody response, and cancer in laboratory animals are supported by human epidemiology studies.

4.1 Noncancer Health Effects

4.1.1 Animal Toxicology

The database of animal toxicology studies is extensive with short-term, subchronic, and chronic toxicity and cancer studies; developmental and reproductive toxicity, neurotoxicity, and immunotoxicity studies; and mechanistic studies.

Developmental Effects

Developmental effects were reported in offspring of rats exposed to PFOS in utero and lactationally, including increased pup mortality (Chen et al. 2012; Lau et al. 2003; Thibodeaux et al. 2003), decreased body weight (Luebker et al. 2005a, 2005b), and developmental delays (Butenhoff et al. 2009). In the two-generation study by Luebker et al. (2005b) pup mortality occurred at 1.6 mg/kg/day and reduced body weight was seen at 0.1 mg/kg/day. Evidence also suggests that PFOS affects lung surfactants in neonates (Chen et al. 2012; Grasty et al. 2003, 2005). This could reflect an impact of PFOS on the phospholipids found in the lung surfactants and required for oxygen uptake in neonates (Xie et al. 2010a, 2010b). Newborn rats and mice exposed to PFOS via maternal lactational transfer developed insulin resistance later in life (Lv et al. 2013; Wan et al. 2014); the effects were more pronounced when the animals were fed a high-fat diet (Wan et al. 2014).

Nervous System Effects

Some neurotoxicity studies show effects on brain development; others found no effects. In studies where rats were placed in a swimming maze, increased escape latency was observed in studies where PFOS was administered by gavage or drinking water (Long et al. 2013; Wang et al. 2015) with LOAELs of 2.15 and 2.4 mg/kg/day. Butenhoff et al. (2009) observed increased motor activity and decreased habituation in animals after gestational and lactation exposure to PFOS. The LOAEL for developmental neurotoxicity in male rats was 1.0 mg/kg/day (Butenhoff et al. 2009) and the NOAEL was 0.3 mg/kg/day. Liao et al. (2009) reported suppression of hippocampal neurite growth and branching, purportedly due to PFOS interference with the phospholipid bilayer of neuronal cells.

Liver Disease and Function

Increased liver weights are the most sensitive hallmark of exposure to PFOS but do not uniformly identify a LOAEL unless accompanied by inflammation, fibrosis, necrosis, or macrovesicular steatosis (Hall et al. 2012). Effects on liver weight were observed at low doses in many studies but were not accompanied by the effects needed to characterize the changes as adverse (Seacat et al. 2002, 2003; Thomford 2002).

Serum Lipids

PFOS induced differential expression of genes involved in lipid metabolism and cholesterol synthesis and transport (Rosen et al. 2010; Tan et al. 2012; L. Wang et al. 2014). These effects are consistent with the demonstration of decreased cholesterol levels, including HDL in rats (Curran et al. 2008; Seacat et al. 2003; L. Wang et al. 2014), very low density lipoprotein (VLDL) in mice (Bijland et al. 2011) and liver retention of triglycerides (i.e., steatosis) (Wan et al. 2012; L. Wang et al. 2014).

Immune Function

Effects on immune response in animals are also associated with PFOS exposure; however, inconsistencies exist across the study results (Dong et al. 2009; Keil et al. 2008; Peden-Adams et al. 2008; Zheng et al. 2009) that highlight the need for additional research to confirm a LOAEL for the immunological endpoints. Among the studies that examined males and females, males consistently responded at lower doses than females.

Thyroid

Reports of thyroid effects varied across studies. In monkeys chronically exposed to low concentrations of PFOS, triiodothyronine (T3) levels were significantly reduced, but a dose-response relationship was not observed (Seacat et al. 2002). In studies using rats, the most consistent finding was a decrease in thyroxine (T4) with little to no change in T3 levels (Chang et al. 2007, 2008; Martin et al. 2007; Yu et al. 2011) and no effect on thyroid-stimulating hormone (TSH) or the hypothalamic-pituitary-thyroid axis (Chang et al. 2008). Overall, thyroid effect observations are inconsistent across studies in primates and rats.

4.1.2 Human Epidemiology Studies

Numerous epidemiology studies evaluating large cohorts of highly exposed occupational and general populations have examined the association of PFOS exposure to a variety of health endpoints. Health outcomes assessed include blood lipid and clinical chemistry profiles, thyroid effects, reproductive and developmental parameters, immune function, and cancer.

Serum Lipids

Multiple epidemiologic studies have evaluated serum lipid status in association with PFOS concentration. These studies provide support for an association between PFOS and small increases in total cholesterol in the general population at mean serum levels of 0.0224 to 0.0361 µg/mL (Eriksen et al. 2013; Frisbee et al. 2010; Nelson et al. 2010). Hypercholesterolemia, which is clinically defined as cholesterol greater than 240 mg/dL, was

associated with PFOS exposure in a Canadian cohort (Fisher et al. 2013) and in the C8 Health Project cohort (a high-exposure community population near a production plant in the U.S.) (Steenland et al. 2009). Cross-sectional occupational studies demonstrated an association between PFOS and total cholesterol (Olsen et al. 2001a, 2001b, 2003). Evidence for associations between other serum lipids and PFOS is mixed including HDL cholesterol, low density lipoprotein (LDL), VLDL, and non-HDL cholesterol, as well as triglycerides.

The studies on serum lipids in association with PFOS serum concentrations are largely cross-sectional in nature and were largely conducted in adults, but some studies exist on children and pregnant women. Limitations to these studies include the frequently high correlation between PFOA and PFOS exposure; not all studies control for other PFASs, such as PFOA, in study design. Also studied were populations with known elevated exposure to other environmental chemicals including PFOA, polybrominated diphenyl ethers (PBDEs), and other persistent chemicals. Overall, the epidemiologic evidence supports an association between PFOS and increased total cholesterol.

Thyroid

Numerous epidemiologic studies evaluated thyroid hormone levels and/or thyroid disease in association with serum PFOS concentrations. These epidemiologic studies provide support for an association between PFOS exposure and incidence or prevalence of thyroid disease, and include large studies of representative samples of the general U.S. adult population (Melzer et al. 2010; Wen et al. 2013). These highly powered studies reported associations between PFOS exposure (serum PFOS concentrations) and thyroid disease. Melzer et al. (2010) reported associations with thyroid disease in men; Wen et al. (2013) saw associations with subclinical hypothyroidism in men and women. In studies of pregnant women, PFOS was associated with increased TSH levels (Berg et al. 2015; Wang et al. 2013). Pregnant women testing positive for the anti-thyroid peroxidase (TPO) biomarker for autoimmune thyroid disease showed a positive association with PFOS and TSH (Webster et al. 2014). In a second study, an association with PFOS and THS and T3 was found in a subset of the NHANES population with both low-iodide status and positive anti-TPO antibodies. Pregnant women testing positive for the anti-TPO biomarker for autoimmune thyroid disease showed a positive association with PFOS and TSH (Webster et al. 2014). In a second study, Webster et al. (2015) found an association with PFOS and THS and T3 in a subset of the NHANES population with both low iodide status and positive anti-TPO antibodies. These studies used anti-TPO antibody levels as an indication of stress to the thyroid system, not a disease state. Thus, the association between PFOS and altered thyroid hormone levels is stronger in people at risk for thyroid insufficiency or disease. In people without diagnosed thyroid disease or without biomarkers of thyroid disease, thyroid hormones (i.e., TSH, T3 or T4) show mixed effects across cohorts.

Studies of thyroid disease and thyroid hormone concentrations in children and pregnant women found mixed effects; TSH was the indicator most frequently associated with PFOS in studies of pregnant women. In cross-sectional studies where thyroid hormones were measured in association with serum PFOS, increased TSH was associated with PFOS exposure in the most cases (Berg et al. 2015; Wang et al. 2013; Webster et al. 2014), but was null in a small study with 15 participants (Inoue et al. 2004). A case-control study of hypothyroxinemia (normal TSH and low free T4) in pregnant women (Chan et al. 2011), did not show associations of

hypothyroxinemia with PFOS exposure; in most other thyroid diseases, T4 and its compensatory TSH co-vary. Increasing PFOS was associated with increased T4 in children aged 1 to 17 years from the C8 cohort (Lopez-Espinosa et al. 2011); PFOS was not associated with hypothyroidism. A small South Korean study examined correlations between maternal PFASs during pregnancy and fetal thyroid hormones in cord blood (Kim et al. 2011). PFOS was associated with increased fetal TSH and with decreased fetal T3 (Kim et al. 2011). Studies of pregnant women show associations between TSH and PFOS; studies in children show mixed results.

Fertility, Pregnancy, and Birth Outcomes

Fetal growth retardation was examined through measures including mean birth weight, low birth weight, and small for gestational (SGA) age. Mean birth weight examined as a continuous outcome was the most commonly examined endpoint for epidemiology studies of serum/cord PFOS exposures. Although three studies were null (Fei et al. 2008a; Hamm et al. 2010; Monroy et al. 2008), birth weight deficits ranging from 29 to 149 grams were detected in five studies (Apelberg et al. 2007; Chen et al. 2015; Darrow et al. 2013; Maisonet et al. 2012; Washino et al. 2009). Larger reductions (from 69 to 149 grams) were noted in three of these studies (Apelberg et al. 2007; Chen et al. 2015; Washino et al. 2009) based on per unit increases in serum/cord PFOS exposures; the lone categorical data showed an exposure-response deficit in mean birth weight up to 140 grams across the PFOS tertiles (Maisonet et al. 2012). Two (Chen et al. 2015; Whitworth et al. 2012) out of four (Fei et al. 2007; Hamm et al. 2010) studies of SGA and serum/cord PFOS exposures showed some suggestion of increased odds ratios (ORs) (range 1.3 to 2.3), while three (Chen et al. 2012; Fei et al. 2007; Stein et al. 2009) out of four (Darrow et al. 2014) studies of low birth weight showed increased risks (OR range: 1.5-4.8). Although a few of these studies showed some suggestion of dose-response relationships across different fetal growth measures (Fei et al. 2007; Maisonet et al. 2012; Stein et al. 2009), study limitations, including the potential for exposure misclassification, likely precluded the ability to adequately examine exposure-response patterns.

A small set of studies observed an association with gestational diabetes (Zhang et al. 2015 [serum measurements of PFOS were preconception]), pre-eclampsia (Stein et al. 2009) and pregnancy-induced hypertension (Darrow et al. 2013) in populations with serum PFOS concentrations of 0.012 to 0.017 µg/mL. Zhang et al. (2015) and Darrow et al. (2013) used a prospective assessment of adverse pregnancy outcomes in relation to PFASs that addresses some of the limitations in the available cross-sectional studies. Associations with these outcomes and serum PFOA also were observed.

Although some suggested association between PFOS exposures and semen quality parameters exists in a few studies (Joensen et al. 2009; Toft et al. 2012), most studies were largely null (Buck Louis et al. 2015; Ding et al. 2013; Joensen et al. 2013; Raymer et al. 2012; Specht et al. 2012; Vested et al. 2013). For example, morphologically abnormal sperm associated with PFOS were detected in three (Buck Louis et al. 2013; Joensen et al. 2009; Toft et al. 2012) out of nine studies (Buck Louis et al. 2015; Ding et al. 2013; Joensen et al. 2013; Raymer et al. 2012; Specht et al. 2012; Vested et al. 2013).

Small increased odds of infertility was found for PFOS exposures in studies by Jørgensen et al. (2014) (OR = 1.39, 95% CI [0.93, 2.07]) and Vélez et al. (2015) (OR = 1.14, 95% CI [0.98, 1.34]). Although one study was null (Vestergaard et al. 2012), PFOS exposures were associated

with decreased fecundability ratios (FRs), indicative of longer time to pregnancy, were noted in studies by Fei et al. (2009) (FR = 0.74, 95% CI [0.58, 0.93]) and in studies by Jørgensen et al. (2014) (FR = 0.90, 95% CI [0.76, 1.07]). Whitworth et al. (2012) data suggested that reverse causality could explain their observation of subfecundity odds of 2.1 (95% CI [1.2, 3.8]) for the highest PFOS quartile among parous women, but a reduced odds among nulliparous women (OR = 0.7, 95% CI [0.4, 1.3]).

A recent analysis of the pooled Danish National Birth Cohort study samples found limited evidence of reverse causality with an overall fecundability ratio of 0.83 (95% CI [0.72, 0.97]) for PFOS exposures, as well as comparable ratios for parous (0.86, 95% CI [0.70, 1.06]) and nulliparous (0.78, 95% CI [0.63, 0.97]) women (Bach et al. 2015). The same authors reported an increased infertility OR of 1.75 (95% CI [1.21, 2.53]) and OR for parous (OR = 1.51, 95% CI [0.86, 2.65]) and nulliparous (OR = 1.83, 95% CI [1.10, 3.04]) women. Although some concern remains about the possibility of reverse causation explaining some previous study results, these collective findings indicate a consistent association with fertility and fecundity measures and PFOS exposures.

Immune Function

A few studies have evaluated associations with measures indicating immunosuppression. Two studies reported decreases in response to one or more vaccines in children aged 3, 5, and 7 years (e.g., measured by antibody titer) in relation to increasing maternal serum PFOS levels during pregnancy, or at 5 years of age (Grandjean et al. 2012; Granum et al. 2013). Decreased rubella antibody concentrations in relation to serum PFOS concentration were found among 12- to 19-year-old children in the NHANES, particularly among seropositive children (Stein et al. 2015). A third study of adults found no associations with antibody response to influenza vaccine (Looker et al. 2014). In the three studies examining exposures in the background range among children (i.e., general population exposures, geometric means < 0.02 µg/ml), the associations with PFOS were also seen with other correlated PFASs, complicating the conclusions drawn specifically for PFOS.

No clear associations were reported between prenatal PFOS exposure and incidence of infectious disease among children (Fei et al. 2010; Okada et al. 2012), although an elevated risk of hospitalization for infectious disease was found among girls, suggesting an effect at the higher maternal serum levels measured in the Danish population (mean maternal plasma levels were 0.0353 µg/mL). With regard to other immune dysfunction, serum PFOS levels were not associated with risk of ever having had asthma among children in the NHANES with median levels of 0.017 µg/mL (Humblet et al. 2014). A study among children in Taiwan with higher serum PFOS concentrations (median with and without asthma: 0.0339 and 0.0289 µg/mL, respectively) found higher odds ratios for physician-diagnosed asthma with increasing serum PFOS quartile (Dong et al. 2013). Associations also were found for other PFASs. Among asthmatics, serum PFOS was also associated with higher severity scores, serum total immunoglobulin E, absolute eosinophil counts, and eosinophilic cationic protein levels.

4.1.3 Noncancer Mode of Action (MOA)

No published cohesive MOA exists that accounts for the varied toxicological properties of PFOS; however, a number of the unique properties of the compound contribute to its toxicity:

- Metabolic stability accompanied by persistence in tissues as an apparent consequence of saturable renal resorption.
- Electrostatic binding to biopolymers, especially proteins, with resultant alterations in conformation and activity (Luebker et al. 2002; Zhang et al. 2009).
- Actual or potential displacement of endogenous/exogenous substances normally bound to serum albumin such as fatty acids, bile acids, pharmaceuticals, minerals, and T3 (D'Alessandro et al. 2013; Fasano et al. 2005; Zhang et al. 2009).
- Renal resorption (Andersen et al. 2006) and biliary excretion that are dependent on unidentified transporters genetically encoded for management of natural substances (endogenous and exogenous) that prolong systemic retention of absorbed PFOS and explain its long half-life.
- Binding to and activating receptors such as PPAR, thereby initiating activation or suppression of gene transcription (Takacs and Abbott 2007; Tan et al. 2012; Rosen et al. 2010).
- Interference with intercellular communication (Hu et al. 2002).

No cohesive MOA has been proposed that explains the impact of PFOS on growth and development of a fetus of a PFOS-exposed dam resulting in low birth weights in the offspring. However, the data demonstrating interactions with cellular receptors that influence upregulation or down regulation of the expression for key genes controlling nutrients required for growth and development could be contributors to low birth weights. Other potential contributors to low birth weight include effects on fetal transport and/or uptake of key nutrients from serum, the placenta and/or maternal milk, along with possible alterations of gap junction intercellular communications in the fetus or neonate. Little data were identified relevant to these parameters. In a human study, T. Zhang et al. (2013) found PFOS in the placenta, cord blood, and amniotic fluid, demonstrating their distribution to the fetus.

The early life neonatal deaths are observed at higher doses than those influencing birth weight; these are proposed to be a consequence of alteration in the structure of lung surfactants (Chen et al. 2012; Grasty et al. 2003, 2005), possibly leading to death because of poor oxygen uptake as is observed in respiratory distress syndrome. Borg et al. (2010) found PFOS levels in the lungs of pups at the end of gestation and on postnatal day (PND) 1 to be higher than those in their dams. PPARα knockout (KO) and 129S1/SvlmJ wild-type mice were evaluated for PFOS-induced developmental toxicity (Abbott et al. 2009). Neonatal survival was significantly reduced by PFOS in both wild-type and KO litters at all doses. wild-type and KO pup birth weight and weight gain from PND 1 to 15 were not significantly affected by PFOS exposure, but relative liver weight of both wild-type and KO pups was significantly increased at the highest dose tested (10.5 mg/kg/day). Delayed (slight) eye opening of was observed in wild-type and KO on PND13 or 14, respectively. The study authors determined that, because effects in wild-type and KO pups were comparable, PFOS-induced neonatal lethality and delayed eye opening are independent of PPARα activation.

Mechanistic investigations of the habituation response observed in Butenhoff et al. (2009) are also lacking; however, toxicokinetic data demonstrate that the levels in the brain of the late gestation fetus and PND1 pups are higher than in their dams (Borg et al. 2010; Chang et al. 2009) suggesting potential developmental vulnerability.

4.2 Cancer

4.2.1 Animal Cancer Bioassays

A single chronic cancer bioassay in animals is available for PFOS (Thomford 2002/Butenhoff et al. 2012).[5] Increased incidence of hepatocellular adenomas in the male (12% at the high dose) and female rats (8% at the high dose) and combined adenomas/carcinomas in the females (10% at the high dose) were observed, but did not display a clear dose-related response. In males only, the serum alanine transaminase (ALT) levels were increased at 14, 27, and 53 weeks. At 105 weeks there was an increase in eosinophilic clear cell foci, and cystic hepatocellular degeneration in males given 2, 5, and 20 parts per million PFOS. Thomford et al. (2002) identified low levels of single cell necrosis in all dose groups (males and females) with a significant increase in incidence at the high dose for males and females. Thyroid and mammary gland tumors were also observed but did not exhibit dose response. Mammary gland tumors had a high background incidence in all dose groups and showed no response to dose. The small number of epidemiology studies of PFOS exposure do not suggest an association with cancer, but the breadth and scope of the studies are not adequate to make definitive conclusions. All genotoxicity studies including an Ames test, mammalian-microsome reverse mutation assay, an *in vitro* assay for chromosomal aberrations, an unscheduled DNA synthesis assay, and mouse micronucleus assay were negative. Epidemiology studies in occupational and general populations did not support any increases in the incidence of carcinogenicity with exposure to PFOS.

4.2.2 Human Epidemiology Studies

Several human epidemiology studies evaluated the association between PFOS and cancers including bladder, colon, and prostate (Alexander et al. 2003; Alexander and Olsen 2007; Mandel and Johnson 1995). A large increase in mortality risk from bladder cancer was demonstrated, and a subsequent study of bladder cancer incidence in the same cohort found rate ratios of 1.5 to 1.9 in the two highest cumulative exposure categories, compared to an internal referent population (Alexander et al. 2003; Alexander and Olsen 2007). The risk estimates lacked precision because the number of cases were limited. Smoking prevalence was higher in the bladder cancer cases, but the analysis did not control for smoking because data were missing for deceased workers, and therefore positive confounding by smoking is a possibility in this analysis. No elevated bladder cancer risk was observed in a nested case-control study in a Danish cohort with plasma PFOS concentrations at enrollment between 0.001 and 0.0131 µg/mL (Eriksen et al. 2009). Other studies that evaluated cancer risk for specific sites (e.g., prostate,

[5] Thomford (2002) is unpublished, but it contains the raw data. Butenhoff et al. (2012) is the published study.

breast) in the general population were inconsistent (Bonefeld-Jørgensen et al. 2011, 2014; Hardell et al. 2014; Innes et al. 2014).

4.2.3 Cancer Mode of Action

The mode of carcinogenic action of PFOS is not clearly understood. Some have concluded based on available data that liver tumors observed in the cancer bioassays can be attributed mostly to the impact of PFOS on peroxisome proliferation based on a hypothesized lower sensitivity of humans to this MOA (Ashby et al. 1994; Rao and Reddy 1996). Some data support the hypothesis that PPARα agonism MOA could be responsible for observed liver tumors in animals. Several studies have demonstrated that PFOS can activate PPARα (Martin et al. 2007; Shipley et al. 2004; Wolf et al. 2008, 2012); however, data are generally lacking for increased cell proliferation. Specifically, no increase in hepatic cell proliferation was detected in the subchronic study (Seacat et al. 2003) or the cancer bioassay (Thomford 2002) of PFOS. Limited necrosis was present in these studies, but did not demonstrate a response to dose. In addition, no subchronic or longer-term studies revealed evidence of preneoplastic foci in the liver.

Short-term genotoxicity assays suggested that PFOS is not a DNA-reactive compound. The results from five *in vitro* studies (Cifone 1999; Litton Bionetics, Inc. 1979; Mecchi 1999; Murli 1999; Simmon 1978) were negative, as was the result from an *in vivo* bone marrow micronucleus assay (Murli 1996).

Other possible MOAs for carcinogenicity have been explored, including mitochondrial biogenetics and gap junctional intercellular communication (GJIC). Although PFOS was shown to be a weak toxicant to isolated mitochondria (Starkov and Wallace 2002), it inhibited GJIC in a dose-dependent manner in two cell lines and in liver tissue from rats exposed orally (Hu et al. 2002). These are not clearly defined MOAs, and their importance relative to PFOS exposure is not certain. Ngo et al. (2014) used the mouse model C57BL/6J –Min/+ for intestinal neoplasia to determine effects following in utero exposure. Maternal treatment with PFOS at doses up to 0.3 mg/kg/day during gestation did not result in an increase of intestinal tumors in either wild type or susceptible offspring up to 20 weeks old.

4.2.4 Weight of Evidence Classification

Under EPA's *Guidelines for Carcinogen Risk Assessment* (USEPA 2005a) there is Suggestive Evidence of Carcinogenic Potential of PFOS in humans based on the liver and thyroid adenomas observed in the chronic rat bioassay (Thomford 2002). The data lack a dose-responsive relationship; thus, they were not used quantitatively in the derivation of a cancer slope factor.

5 DOSE-RESPONSE ASSESSMENT

As an initial step in the dose-response assessment, EPA identified a suite of animal studies with serum information for NOAELs and/or LOAELs that identified them as potential candidates for development of the RfD for PFOS. These studies included subchronic, and developmental and reproductive toxicity studies, one with a neurodevelopmental component. The available studies observed endpoints including increased serum ALT and blood urea nitrogen (BUN),

body weight changes in adults and offspring, reproductive outcomes (e.g., gestation length), and developmental effects (e.g., survival and neurological changes). The candidate studies were selected based on their NOAEL and/or LOAEL, durations of 19 to 98 days, use of a control, and two or more doses. From these studies, those that presented serum data amenable for modeling (i.e., determination of HEDs) were selected for dose-response analysis. The subset of studies amenable for use in derivation of HED based on average serum measurements from the pharmacokinetic model is limited because of the need to have dose and species-specific serum values for model input, as well as exposure durations of sufficient length to achieve values near to steady-state projections or applicable to developmental endpoints with lifetime consequences following short-term exposures. The pharmacokinetically modeled average serum values from the animal studies are restricted to the animal species selected for their low-dose response to oral PFOS intake.

As described in section 3.2.4, EPA used the Wambaugh et al. (2013) pharmacokinetic model to derive the average serum concentrations associated with the candidate NOAELs and LOAELs from the toxicological database. Studies with serum information for each of the doses that demonstrated dose response and were amendable for modeling of the area under the curve (AUC) at the time of sacrifice were used. The AUC results were converted to average serum values at the time of sacrifice with consideration of the duration of exposure. The average serum values were converted to the HED, as described further below.

The data were analyzed within a Bayesian framework using a Markov Chain Monte Carlo sampler implemented as an R package developed by EPA to allow predictions across species, strains, and genders, and to identify serum levels associated with the external doses at the NOAEL and LOAEL. The model predictions were evaluated by comparing each predicted final serum concentration to the serum value measured in the supporting animal studies.

Average serum PFOS concentrations were derived from the AUC considering the number of days of exposure before sacrifice. The predicted serum concentrations are converted into an oral equivalent dose by recognizing that, at steady state, clearance from the body equals the dose to the body. Clearance (CL) can be calculated if the rate of elimination (derived from half-life) and the volume of distribution are both known. EPA used the Olsen et al. (2007) calculated human half-life of 5.4 years and the Thompson et al. (2010) volume of distribution (Vd) of 0.23 L/kg body weight (bw) to determine a clearance of 8.1×10^{-5} L/kg bw/day using the following equation:

$$\text{CL} = \text{Vd} \times (\ln 2 \div t_{½}) = 0.23 \text{ L/kg bw} \times (0.693 \div 1971 \text{ days}) = 0.000081 \text{ L/kg bw/day}$$

Where:

Vd = 0.23 L/kg
ln 2 = 0.693
$t_{½}$ = 1971 days (5.4 years x 365 days/year = 1971 days)

Multiplying the derived average serum concentrations (in µg/mL) for the NOAELs and LOAELs identified in the key animal studies by the clearance value predicts oral HEDs in mg/kg/day for each corresponding serum measurement. The HED values are the predicted human oral exposures necessary to achieve serum concentrations equivalent to the NOAEL or LOAEL in the animal toxicity studies using linear human kinetic information.

The NOAEL, LOAEL, and effect information from those studies, along with the associated average serum values and the percent of steady state represented by the LOAEL, are provided in Table 5-1.

Table 5-1. Human Equivalent Doses Derived from the Modeled Animal Average Serum Values

Study	Dosing duration days	NOAEL mg/kg/d	NOAEL Av serum µg/mL	HED mg/kg/d	LOAEL mg/kg/d	LOAEL Av serum µg/mL	HED mg/kg/d
Seacat et al. (2003): male rat ↑ALT, ↑BUN	98	0.34	16.5	0.0013	1.33	64.6	0.0052
Luebker et al. (2005b): ↓ rat pup body weight	84	0.1	6.26	0.00051	0.4	25	0.002
Luebker et al. (2005a): ↓ rat pup body weight	63	None	None	None	0.4	19.9	0.0016
Luebker et al. (2005a): rat ↓ maternal body weight, gestation length, and pup survival	63	0.4	19.9	0.0016	0.8	39.7	0.0032
Butenhoff et al. (2009): rat DNT (↑motor activity; ↓habituation)	41	0.3	10.4	0.00084	1.0	34.6	0.0028
Lau et al. (2003): ↓rat pup survival; ↓maternal and pup body weight	19	1.0	17.6	0.0014	2.0	35.1	0.0028

Notes:
ALT = alanine transaminase; BUN = blood urea nitrogen; DNT = developmental neurotoxicity; NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; HED = human equivalent dose

The external doses in each of the studies varied. The NOAELs ranged from 0.1 to 1 mg/kg/day. The corresponding average serum values range from 6.26 µg/mL (rat) to 19.9 µg/mL (monkey). At the LOAEL, the average serum values range from 19.9 µg/mL (rat) to 64.6 µg/mL (rat) at doses estimated to represent about 9% to 50% of steady state. At the low end of the range, the effects of concern are observed in neonates (e.g., low birth weight, developmental neurotoxicity). The systemic effects on the liver and kidney occur at the higher serum levels and after longer exposure durations.

Some of the variability is related to the differences in study methodology used in reproductive/developmental studies compared to studies designed to identify effects of long-term exposure on organs, tissues, and the serum biomarkers for effects (e.g., ALT, BUN). There is a five-fold difference in the lowest to highest LOAEL and approximately a three-fold difference in serum values providing support that the studies, despite the differences in species, design, and endpoints evaluated, are representative of low dose-effects levels from studies with clear dose-response across the entire dose range.

5.1 Uncertainty Factors

An uncertainty factor for intraspecies variability (UF_H) of 10 is assigned to account for variability in the responses within the human populations because of both intrinsic (e.g., genetic, life stage, health status) and extrinsic (e.g., life style) factors that can influence the response to exposure. No information was available relative to variability in the human population that supports a factor other than 10.

An uncertainty factor for interspecies variability (UF_A) of 3 was applied to account for uncertainty in extrapolating from laboratory animals to humans (i.e., interspecies variability). The three-fold factor is applied to account for toxicodynamic differences between the animals and humans. The HEDs were derived using average serum values from a model to account for pharmacokinetic differences between animals and humans.

An uncertainty factor for LOAEL to NOAEL extrapolation (UF_L) of 1 was applied to all PODs, except the LOAEL of 0.4 mg/kg/day for effects on pup body weight in the one-generation Luebker et al. (2005a) study. A value of 3 is assigned for this study because the NOAEL for this same effect was 0.1 mg/kg/day in the two-generation (Luebker et al. 2005b) study, a dose that was not used in the one-generation study. The LOAEL in the two-generation study was 0.4 mg/kg/day, demonstrating that the difference between a NOAEL and LOAEL for the body weight is not a factor of 10, the default value for NOAEL/LOAEL extrapolation.

An uncertainty factor for extrapolation from a subchronic to a chronic exposure duration (UF_S) of 1 was applied because the PODs are based on average serum concentrations for all studies except Seacat et al. (2013). The studies for developmental endpoints are not adjusted for lifetime exposures because they cover a critical window of exposure with lifetime consequences. The average serum value associated with the developmental (Luebker et al. 2005b) POD is lower than that for any of the other modeled studies, including those with systemic effects after longer exposures; accordingly, it is more protective of adverse effects than the POD for any of the longer-term studies, despite the limited exposure duration. The serum from the Seacat et al (2013) study was collected at 14 weeks. Some of the animals in the study continued to be dosed for a total of 105 weeks, but the effects observed at the LOAEL did not increase in magnitude. Serum measurements taken before sacrifice were two-fold higher at 14 weeks in males than they were at 105 weeks. Concentrations of PFOS in the liver were lower at 105 weeks than they were at 14 weeks. The PFOS concentrations in the diet were constant. Standard deviations about the monitored ALT and BUN were broad, indicating higher sensitivity is some animals than others. The serum and effects data for the male rats justify a 1 for the subchronic to chronic adjustment to the study NOAEL.

A database uncertainty factor (UF_D) of 1 was applied to account for deficiencies in the database for PFOS. The epidemiology data provide strong support for the identification of hazards observed following exposure to PFOS in the laboratory animal studies and human relevance. Uncertainties in the use of the available epidemiology data, however, precluded their use at this time in the quantification of the effect level for derivation of the drinking water HA. 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. In addition, 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).

5.2 RfD Determination

Table 5-2 provides the calculations for potential RfDs using the HEDs derived from the NOAEL or LOAEL average serum concentrations using pharmacokinetic modeling based on the serum values measures collected at animal sacrifice. Uncertainty factors (see section 5.1) were applied to each POD; Table 5-2 illustrates the array of candidate RfD outcomes. Each POD is impacted by the doses used in the subject study, the endpoints monitored, and the animal species/gender studied; therefore, the array of outcomes, combined with knowledge of the individual study characteristics, helps inform selection of an RfD that will be protective for humans. It is important to note the relatively narrow range of RfDs across the multiple endpoints and study durations evaluated.

Table 5-2. Candidate RfDs Derived from HEDs from the Pharmacokinetic Model Average Serum Values

POD	HED POD mg/kg/day	UF_H	UF_A	UF_L	UF_S	UF_D	UF_{total}	Candidate RfD mg/kg/day
(Seacat et al. 2003): male rat NOAEL for ↑ALT, ↑BUN	0.0013	10	3	1	1	1	30	0.00004
PK-HED (Lau et al. 2003): rat, NOAEL for ↓ pup survival and body weight	0.0014	10	3	1	1	1	30	0.00005
PK-HED (Butenhoff et al. 2009): rat, NOAEL for ↑motor activity ↓habituation	0.00084	10	3	1	1	1	30	0.00003
PK-HED (Luebker et al. 2005b): rat, NOAEL for ↓pup body weight	0.00051	10	3	1	1	1	30	0.00002
PK-HED (Luebker et al. 2005a): rat, NOAEL for ↓pup survival	0.0016	10	3	1	1	1	30	0.00005
PK-HED LOAEL (Luebker et al. 2005a): rat, LOAEL for ↓pup body weight	0.0016	10	3	3	1	1	100	0.00002

Notes:
PK-HED = pharmacokinetic human equivalent dose; NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; UF_H = intra-individual uncertainty factor; UF_A = interspecies uncertainty factor; UF_S = subchronic to chronic uncertainty factor, UF_L = LOAEL to NOAEL uncertainty factor; UF_D = incomplete database uncertainty factor; UF_{total} = total (multiplied) uncertainty factor

Using the pharmacokinetic model of Wambaugh et al. (2013), average serum PFOS concentrations were derived from the AUC considering the number of days of exposure before sacrifice. The predicted serum concentrations were converted, as described above, to oral HEDs mg/kg/day for each corresponding serum measurement. The candidate RfDs in Table 5-2 range

from 0.00002 to 0.00005 mg/kg/day across multiple endpoints. The RfD of 0.00002 mg/kg/day calculated from HED average serum values from Luebker et al. (2005b) was selected. This RfD is derived from reduced pup body weight in the two-generation study in rats. The POD for the derivation of the RfD for PFOS is the HED of 0.00051 mg/kg/day that corresponds to a NOAEL that represents approximately 30% of steady-state concentration. A UF of 30 (10 UF_H and 3 UF_A) was applied to the HED NOAEL to derive an RfD of 0.00002 mg/kg/day. This is supported by the 0.00002 mg/kg/day value derived from the LOAEL for the same effect in the one-generation Luebker et al. (2005a) study and the 0.00003 mg/kg/day value for neonatal neurodevelopmental effects in the Butenhoff et al. (2009) study.

Low body weights in neonates are a biomarker for developmental deficits, and are linked to problems that often manifest later in life. A study by Lv et al. (2013) that lacked serum data for pharmacokinetic modeling identified 0.5 mg/kg/day as a LOAEL for effects on body weight in Wistar rat pups exposed during gestation, an observation that was accompanied by increased insulin resistance, problems with glucose homeostasis, and hepatic fat accumulation in the pups as adults. A similar effect on glucose homeostasis was observed in CD-1 mice at PND 63 in a study by Wan et al. (2014) with a dose of 3 mg/kg/day for animals receiving a diet with regular fat content. For animals receiving a high-fat diet, the LOAEL was 0.3 mg/kg/day. Support for the neurodevelopmental effects in Butenhoff et al. (2009) at a dose of 1 mg/kg/day kg/day is provided by the NOAEL (0.43 mg/kg/day) in the Long et al. (2013) 90-day mouse study for effects on learning and memory.

6 HEALTH ADVISORY VALUES

6.1 Relative Source Contribution

As described in section 2.2 and below, humans can be exposed to PFOS via multiple sources, including air, food, and consumer and industrial products (including textiles and rugs). The most common route of exposure to PFOS is via the diet, followed by indoor dust, especially for children.

Food is a significant source of exposure to PFOS; it has been detected in a variety of foods, including eggs, milk, meat, fish, root vegetables, and human breast milk. Occurrence in food products can result from the use of contaminated water in processing and preparation; growth of food in contaminated soils; direct and indirect exposures of domestic animals to PFOS from drinking water, consumption of plants grown in contaminated soil, and through particulate matter in air; fish from contaminated water ways; and packaging materials.

PFOS has been detected in finished drinking water samples collected by EPA and others. PFOS is not regulated under the SDWA and was included in EPA's UCMR 3. PFOS was detected at a small number of PWSs (2%) through this monitoring program. Therefore, potential exposure to PFOS could occur from ingesting drinking water.

The vapor pressure of PFOS indicates that volatilization is low; however, PFOS can be released into the atmosphere from industrial and municipal waste incinerators and adsorb to airborne particulates. It can be transported long distances via the atmosphere and has been detected globally at low concentrations. Inhalation of PFOS is possible; it has been measured in

indoor air in residential, commercial, and office settings because of its use in carpets, textiles, paint, furniture, and other consumer products. Both air and dust can be a vehicle for volatile PFOSA precursors that metabolically degrade to PFOS. Given the widespread commercial and industrial use of PFOS, as well as its physical properties, air is a potential source of exposure.

PFOS has also been detected in soils and dust from carpets and upholstered furniture in homes, offices, and vehicles. Incidental exposure from soils and dust is an important exposure route, particularly for small children because of their hand-to-mouth behaviors. Also, the levels in soils and surface waters can affect the concentrations in local produce, meat/poultry, dairy products, fish, and particulates in the air.

In summary, based on the physical properties and available exposure information regarding PFOS, there are many potentially significant sources. Following EPA's Exposure Decision Tree in its 2000 Methodology (USEPA 2000b), significant potential sources other than drinking water ingestion exist; however, information is not available to quantitatively characterize exposure from all of these different sources (Box 8B in the Decision Tree). Therefore, EPA recommends an RSC of 20% (0.20) for PFOS.

6.2 Lifetime Health Advisory

Based on the consistency of responses across studies and endpoints, and recognizing the use of developmental toxicity as the sensitive endpoint, 0.00002 mg/kg/day was selected as the RfD for PFOS. This value is based on the HED for developmental effects (e.g., decreased pup body weight) from the Luebker et al. (2005b) study. The RfD that serves as the POD for the lifetime HA is applicable for effects other than those occurring during development. The candidate RfD (0.00002 mg/kg/day) derived from the HED LOAEL for the same effect in the one-generation Luebker et al. (2005a) study and the candidate RfD (0.00003 mg/kg/day) for neonatal neurodevelopmental effects in the Butenhoff et al (2009) study provide additional support for the selection of the Luebker et al. (2005b) two generation study.

Because of the potential increased susceptibility during pregnancy and lactation, EPA used drinking water intake and body weight parameters for lactating women to calculate a lifetime HA for this target population during this potential critical time period. EPA used the rate of 54 mL/kg-day to represent the consumers-only estimate of combined direct and indirect community water ingestion at the 90^{th} percentile for lactating women (see Table 3-81 in U.S EPA 2011b). Comparing between the pregnant and lactating woman, the lactating woman is provided with the more protective scenario, given her increased water intake rate for her body weight needed to support milk production. Additionally, human studies have shown that PFOS is transferred from mother to infant via cord blood and breast milk. A recent study showed that breast milk contributed > 94% of the total PFOS exposure in 6-month-old infants (Haug et al. 2011).

The exposure factors applied to the RfD to derive the lifetime HA are specific to the most sensitive population, and will be protective of pregnant women and the general population. Thus, the protection conferred by the lifetime HA is broadly protective of public health.

The lifetime HA for PFOS is calculated as follows:

A Drinking Water Equivalent Level (DWEL) is derived from the RfD. The DWEL assumes that 100% of PFOS exposure comes from drinking water.

$$\text{DWEL} = \frac{\text{RfD x bw}}{\text{DWI}}$$

$$\text{DWEL} = \frac{0.00002 \text{ mg/kg/day}}{0.054 \text{ L/kg/day}} = 0.00037 \text{ mg/L}$$

Where:

RfD = 0.00002 mg/kg/day; based on the NOAEL for decreased pup body weight in rats, where dams were exposed by gavage 6 weeks prior to mating, during mating, and through gestation and lactation (Luebker et al. 2005b).

DWI/bw = 0.054 L/kg/day; 90th percentile consumers-only estimate of combined direct and indirect community water ingestion for lactating women (see Table 3-81 in USEPA 2011b).

The lifetime HA is calculated after application of a 20% RSC (see section 6.1) as follows:

Lifetime HA = DWEL x RSC
= 0.00037 mg/L x 0.2
= 0.000074 mg/L (rounded to 0.00007 mg/L)
= 0.07 µg/L

The lifetime HA for PFOS is based on effects (e.g., pup body weight) on the developing fetus resulting from exposures that occur during gestation and lactation. These developmental endpoints are the most protective for the population at large and are effects that could carry lifetime consequences for a less-than-lifetime exposure. Developmental toxicity endpoints (following less-than-chronic exposures during a defined period of gestation or lactation) can be analyzed in both acute and chronic exposure scenarios. Because the developing organism is changing rapidly and is vulnerable during various stages in development, a single exposure at a critical time in development might produce an adverse effect (USEPA 1991). PFOS is extremely persistent in both the human body and the environment; thus, even a short-term exposure results in a body burden that persists for years and can increase with additional exposures.

Because the critical effect identified for PFOS is a developmental endpoint and can potentially result from a short-term exposure during a critical period of development, EPA concludes that the lifetime HA for PFOA is applicable to both short-term and chronic risk assessment scenarios. Thus, the lifetime HA of 0.07 µg/L also applies to short-term exposure scenarios (i.e., weeks to months) to PFOA in drinking water, including during pregnancy and lactation.

Adverse effects observed following exposures to PFOA and PFOS are the same or similar, and include effects on serum lipids, birth weight, and antibodies in humans. The animal studies include common effects on the liver, neonate development, and responses to immunological challenges. Both compounds were also associated with tumors in long-term animal studies. The

effects serving as the basis for the RfDs for both PFOA and PFOS are developmental endpoints (e.g., reduced ossification and accelerated puberty in males for PFOA and decreased pup birth weight for PFOS; see USEPA 2016a, 2016b). Because the RfDs for both PFOA and PFOS are based on similar developmental effects and are numerically identical, when these two chemicals co-occur at the same time and location in a drinking water source, a conservative and health-protective approach that EPA recommends would be to compare the sum of the concentrations ([PFOA] + [PFOS]) to the HA (0.07 μg/L).

7 CANCER RISK

When the evidence from the epidemiology studies and the cancer bioassays is sufficient to determine there is Suggestive Evidence for Carcinogenic Potential, EPA generally does not attempt a quantitative dose-response assessment unless a well-conducted study exists that could provide a sense of the magnitude and uncertainty of potential risks, help rank potential hazards, or help establish research priorities. In the case of PFOS, the weight of evidence for relevance to humans was judged as too limited to support a quantitative assessment. Additionally, modeling of the liver and thyroid adenomas observed in the chronic rat bioassay (Thomford 2002) was not possible because there was no dose-response.

8 EFFECTS CHARACTERIZATION

8.1 Uncertainty and Variability

The variability and uncertainty in the lifetime HA is a function of both intrinsic and extrinsic factors. EPA's HESD for PFOS (USEPA 2016b) identified 21 short- or long-term studies that provided dose-response information; these were considered during the risk assessment. Of those, only five studies included the serum data necessary to ultimately derive HEDs for use as the POD for the RfD. The range of external dose NOAELs among the 21 studies is 0 to 1 mg/kg/day and the LOAEL range is 0.00017 to 5 mg/kg/day (USEPA 2016b). Six dose-response data sets included the serum data necessary for modeling to derive HEDs for use as the POD for the RfD. Average serum values from those studies were used to derive the RfD. The external dose range for the NOAELs in the modeled studies is 0.1 to 1 mg/kg/day and the LOAEL range is 0.4 to 2 mg/kg/day (USEPA 2016b). EPA believes the uncertainty in the chosen POD and the reliance on studies with serum data is minimized because of the large and extensive database examining hazard, and the selection of pup body weight as the critical effect with lifetime implications at a NOAEL (0.1 mg/kg/day) from the low end of the range of values evaluated.

The intrinsic uncertainties in the assessment reflect the fact that the NOAELs and LOAELs are derived using central-tendency estimates for variables such as body weight, food and drinking water intakes, and dose. In addition, the estimates are derived from small numbers of genetically similar animals representing one or more strains of monkeys, rats, or mice living in controlled environments. The animals lack the heterogeneous genetic complexity, behavioral diversity, and complex habitats experienced by humans. These differences, to some extent, are minimized through consideration of the modeled central-tendency outcomes and their standard deviations to help inform the application of the uncertainty factors.

Variability in the study outcomes is extrinsically a function of study design and the endpoints monitored. Systemic toxicity studies monitor an array of endpoints not evaluated in studies of reproductive, developmental, neurological and immunological toxicity. The reverse is true for the other types of toxicity studies compared to standard short- to long-term systemic studies. Studies of systemic toxicity do not often examine neurological or immunological endpoints. Increases in liver weight were seen in many of the studies with dose-response information, but only a few of the studies carried out a histological evaluation of the liver to support a determination of whether the increase in liver weight could be classified as adverse according to the Hall et al. (2012) criteria.

The RfD is based on the HED derived from serum levels at the NOAEL from a developmental study in rats (Luebker et al. 2005b), with the application of an uncertainty factor of 30 to cover variability in the human population and differences in the ways humans respond to the PFOS that reaches their tissues compared to rats. The selected RfD is based on the most sensitive endpoint, developmental effects (e.g., decreased pup body weight), to provide protection to the general population and sensitive life stages. The RfD is supported by the outcomes from two other studies (Butenhoff et al. 2009; Luebker et al. 2005a) with RfD outcomes that are the same or slightly higher than the chosen RfD, thereby increasing the confidence in the RfD. The candidate RfD of 0.00004 mg/kg/day derived from the NOAEL for systemic toxicity (e.g., liver damage, potential effects on the kidney) in male rats (Seacat et al. 2003) after a 14-week exposure shows that the RfD derived for the developmental effects also is protective for effects on the liver and kidney.

8.2 Use of Epidemiology Data

The human epidemiology studies provide evidence of an association between PFOS exposure and health effects in humans, and is another line of evidence supporting this assessment. The human data demonstrate an association between PFOS exposure and endpoints including effects on serum lipids, antibody responses, the thyroid, and fetal growth and development. The data provide support for identification of hazards of PFOS exposure. The associations observed for serum lipids and reproductive outcomes are the strongest. For many endpoints, the results are inconsistent, however. Although the human studies collectively support the conclusion that PFOS exposure is a hazard, EPA concluded that based on several uncertainties associated with the database, the human studies are adequate for use qualitatively in the identification hazard at this time. These considerations are discussed below.

Although mean serum values are presented in the human studies, actual estimates of exposure (i.e., doses/duration) are not available. Thus, the serum level at which the effects were first manifest, and whether the serum had achieved steady state or was in decline at the point the effect was evaluated, cannot be determined. The NHANES data indicate that serum levels in the general population are declining. Because epidemiology data reflect the serum concentration at the time the sample was collected, it is not possible to determine if levels were previously higher and had decreased.

Although the epidemiology studies provide valuable associations between exposure to PFOS and the effects seen in animal studies, most of the subjects of the epidemiology studies had other perfluorinated carboxylates and sulfonates and/or other biopersistent contaminants in their blood.

Although the study designs adjusted for other potential toxicants as confounding factors, their presence constitutes a level of uncertainty that is usually absent in animal studies.

Interspecies and gender variation in PFOS clearance half-life can vary by several orders of magnitude. If the toxicological endpoints are assumed to be driven by internal concentrations, then it is the internal exposure that is calculated and considered across species. Differences in pharmacokinetics across species produce differences in the external dose needed to achieve the same internal dose. The use of the animal data and the available pharmacokinetic model allows for the incorporation of species differences in saturable renal resorption, dosing duration, and serum measurements to determine HEDs based on average serum concentration and clearance. The potential for confounding influences is decreased under the controlled conditions of the animal studies. Applying uncertainty factors when deriving the RfD acknowledges the limitations associated with the use of the animal serum information.

The PFOA database includes extensive human data from epidemiology studies from the general population as well as worker cohorts. Data from oral short-term, subchronic, chronic (including evaluation of cancer), reproductive, and developmental studies in laboratory animals are also available. Many of the effects observed in the human epidemiology studies are similar to those seen in the animal studies.

8.3 Consideration of Immunotoxicity

Both human and animal studies have demonstrated the potential impact of PFOS on the immune system; however, uncertainties exist related to MOA and the level, duration, and/or timing of exposure that are not yet clearly delineated. The animal immunotoxicity studies support the association between PFOS and effects on the response to sheep red blood cells as foreign material and on the natural killer cell populations; however, the doses with effects are inconsistent across studies for comparable endpoints. When both males and females were evaluated, the males responded at a lower dose than the females. Because of these uncertainties, EPA did not quantitatively assess this endpoint.

Taken together, available human studies (Grandjean et al. 2012; Granum et al. 2013; Looker et al. 2014) provide some evidence of a significant association between PFOS exposure and serological vaccine responses in general. Within each study, however, most estimated associations were statistically nonsignificant, and results were inconsistent by vaccine type and by outcome classification. Authors provided no *a priori* biological hypothesis to explain why PFOS exposure would impair the antibody response to one vaccine type but not another. Some authors suggested that their results could be explained by different immunostimulatory effects of different vaccines, but they did not elaborate on this hypothesis nor provide supporting mechanistic evidence.

One issue related to use of immune biomarkers and antibody levels in human studies is whether small but statistically significant changes in these endpoints, when analyzed on a continuous scale, are clinically meaningful, particularly when most or all subjects are within the normal range. For PFOS, some studies attempted to address this issue by analyzing outcomes dichotomized relative to standard reference values, with the implication that values outside the reference range indicate immune abnormalities (Dong et al. 2013; Grandjean et al. 2012; Granum et al. 2013). A limitation of this approach is that a reference range is typically

determined based on the mean, plus or minus two standard deviations, calculated from a group of healthy adults or children. By definition, 5% of the normal population falls outside of such a reference range (AACC 2015). The only way to determine whether a given value outside a reference range is truly ‘‘abnormal’’ is to associate it with a clinical abnormality, yet this has not been done in most epidemiologic studies of immune biomarkers.

Another limitation of epidemiology studies that evaluate the immune response following PFOS exposure is that these studies have not demonstrated whether immune parameters measured in clinically normal individuals accurately reflect the risk of future immunological diseases. Given the immune system's capacity for repair and regeneration, apparent abnormalities that are detected at one point in time might resolve before producing any adverse clinical health effect. Thus, biomarkers that do not accurately diagnose or predict the presence or absence of a clinical health condition are not clinically useful. Maternal prenatal serum PFOS levels generally were not associated with a significant difference in the tetanus vaccine response. Maternal PFOS levels were generally associated with a poorer childhood diphtheria vaccine response, as measured based on antibody titers and the presence of a possibly nonprotective antibody level, although most differences were statistically nonsignificant. Decreased rubella antibody concentrations in relation to serum PFOS concentration were found among 12- to 19-year-old children in the NHANES, particularly among seropositive children (Stein et al. 2015).

Although Grandjean et al. (2012) found fairly consistent, albeit mostly statistically nonsignificant, intra-study associations between childhood serum PFOS levels and poorer antibody responses against tetanus and diphtheria toxoids, associations with maternal prenatal serum PFOA and PFOS levels were inconsistent between vaccine types. Two studies were strengthened by their measurement of PFOS levels before ascertaining vaccine response (Grandjean et al. 2012; Granum et al. 2013); one had the additional advantage of collecting exposure and outcome information at two time points each (Grandjean et al. 2012). However, the variability in findings by timing of exposure and outcome measurement in the latter study (e.g., mostly nonsignificant associations with prenatal PFOS concentrations, but several significant associations between higher PFOS concentrations at age 5 years and poorer vaccine response at age 7 years) makes the results difficult to interpret. This pattern of results could reflect a window of susceptibility in early childhood, but such an explanation remains conjectural.

None of the studies demonstrated a clinically recognizable increased risk of infectious diseases as a consequence of a diminished vaccine response. Overall, although these results are not sufficient to establish a causal effect of PFOS exposure on an impaired serological vaccine response, some of the positive associations are striking in magnitude and require replication in independent studies.

Chang et al. (2016) recently completed and published a systematic review of 24 epidemiology studies that reviewed a variety of endpoints among the general population, occupationally exposed workers, children, and adults, and concluded that the available epidemiologic evidence is insufficient to reach a conclusion about a causal relationship between exposure to PFOA and PFOS and any immunity-related health condition in humans. The majority of studies reviewed by the authors are included in EPA's HESDs for PFOA and PFOS (USEPA 2016a, 2016b). The authors identified numerous weaknesses in the study designs, including failing to validate self-reported medical conditions, basing conclusions on significant associations without considering statistical significance, and not adequately considering

confounding factors, bias, and the role of chance being responsible for outcomes. After applying the Hill et al. (1965) criteria, they faulted the studies for "generally weak associations, no specific endpoints with consistent findings across all relevant studies, uncertainty about any critical duration of exposure and window(s) of susceptibility, mixed exposure-response trends, and a dearth of supportive animal and mechanistic data."

A need remains for additional research on MOA, key biomarkers that are reliable indicators for the upstream effects elicited by PFASs, the temporal relationship between exposure and outcome plus the analytical and functional impact of PFAS binding to serum immunoglobins and/or related proteins.

8.4 Alternative Exposure Scenarios

EPA is issuing a lifetime HA for PFOS of 0.07 µg/L to prevent a variety of adverse developmental effects to fetuses during pregnancy and to infants during breast feeding. Due to the potential increased susceptibility during this critical time period, EPA used drinking water intake and body weight parameters for lactating women to calculate the lifetime HA (see section 6.2). Specifically, EPA used the rate of 54 mL/kg-day representing the consumers only estimate of combined direct and indirect community water ingestion at the 90th percentile for lactating women (see Table 3-81 in [U.S EPA 2011b]).

As a comparative analysis, EPA calculated a lifetime HA value for alternative exposure scenarios for the general population. Calculation of a lifetime HA value for the general population (adults ages 21 and older) is 0.1 µg/L, assuming a drinking water rate of 2.5 L/day and a mean body weight of 80 kg (see Tables 3-33 and 8-1 in [U.S EPA 2011b]).

PFOS is extremely persistent in both the human body and the environment; thus, even a short-term exposure results in a body burden that persists for years and can increase if additional exposure occurs later. Human studies have shown that PFOS is transferred from mother to infant via cord blood and breast milk. The exposure scenario for the lactating woman is the most protective given her increased water intake rate to support milk production and thus is the basis for EPA's recommended lifetime HA for PFOA of 0.07 µg/L. The lifetime HA for PFOS is also protective of adverse health effects in the adult general population (e.g., liver damage, other developmental effects, and developmental neurotoxicity).

8.5 Relative Source Contribution Considerations

EPA used the Exposure Decision Tree methodology (USEPA 2000b) to derive the RSC for this HA. Findings from studies on populations in the United States, Canada, and Western Europe support the conclusion that diet is the major contributor to total PFOS exposure, typically with drinking water and/or dust as important additional exposure routes, especially for sensitive subpopulations. Estimates of relative exposure from different sources vary widely, as described below.

- Tittlemier et al. (2007) conducted a total diet study, focused on collection and analysis of different food items. They concluded that diet represented approximately 60% of total PFAS exposure, with a negligible contribution from drinking water, based on samples collected from two cities in Canada.

- Egeghy and Lorber (2011) used models to estimate exposures for adults and 2-year-olds. For a typical exposure scenario, they estimated that dietary ingestion is the major contributor of PFOS to adults. Dietary and dust ingestion were nearly equal contributors to PFOS exposure in young children. Based on an estimate of a low concentration in drinking water (median of 21 ng/L), the authors estimated PFOS exposure from drinking water at approximately 22% of total intake for both adults and children. As background concentrations of PFOS in water increase, drinking water represents a greater source of total dietary intake.
- Jogsten et al. (2012) estimated that about 93% of the PFOS exposure in Catalonia Spain was from diet for adults and 6.5% from drinking water for adults; for toddlers, 97% was from diet and 2.5% was from drinking water.
- Gebbink et al. (2015) estimated the relative contributions of the major exposure media to total direct and indirect PFOS exposures under assumptions of low (5^{th} percentile), intermediate (median values), and high (95^{th} percentile) exposures. The authors used a Scenario-Based Risk Assessment modeling approach with data collected in 2007 to estimate the relative contributions to total exposures. The data for direct and indirect contributors to serum PFOS (presented graphically in the published paper) are consistent with the following patterns for exposures in adults:
  - Low exposure scenario = diet (~88%) > air (~7%) > water (~3%) > dust (~2%)
  - Intermediate exposure scenario = diet (~65%) > dust (14%) ≈ air (14%) > water (~7%)
  - High exposure scenario = diet (~43%) > dust (27%) > air (20%) > water (~10%).

The approaches and assumptions used in these studies vary widely; some uncertainties associated with these data include:

- Many of the data are obtained from review papers or individual studies conducted at single locations and are not nationally representative.
- Concentrations range widely in exposure estimates.
- The ambient air and dust exposure estimates are limited, regional, and variable.
- Drinking water exposure varies among age groups and individuals.
- Because of recent reductions in use of PFOS, assessing current relative exposures to the general population is difficult.

Additionally, data on other routes of exposure are lacking:

- Estimates of dermal exposure to treated fabrics and inhalation exposure associated with contaminated water are not available.
- Drinking water exposure estimates apply only to direct ingestion of tap water and beverages or soups prepared locally. They do not generally include PFOS in water that becomes incorporated in solid foods during home preparation and cooking, or that which is present in commercial beverages.
- Transformation of PFOSA precursors that decay or are metabolized to PFOS is a route that is rarely evaluated in dietary studies, yet can contribute to total exposure. Air and dust can be vehicles for PFOSA derivatives that metabolically degrade to PFOS.

Given these uncertainties, EPA used the Exposure Decision Tree methodology (described in section 7.1 of USEPA 2000b) to estimate an RSC of 20% for drinking water for the general population.

8.6 Sensitive Populations: Gender Differences

Male monkeys were slightly more sensitive to PFOS than females, as indicated by early deaths in two of six males (compared to no female early deaths) and a greater reduction in the male body weight. Male rats were more susceptible to liver damage than females (Butenhoff et al. 2012; Seacat et al. 2003; Thomford 2002). Both males and females seem to be equally sensitive to thyroid hormone effects in the studies by Curran et al. (2008) and Seacat et al. (2002). In animal studies of immunological effects, the response to natural killer cell suppression occurred at a lower dose in males than in females (Keil et al. 2008; Peden-Adams et al. 2008).

8.7 Sensitive Populations: Developmental Effects

Animal studies show that developmental exposure of rats or mice to PFOS administered during gestation results in rapid, dose-dependent effects on neonatal survival (Lau et al. 2003; Luebker et al. 2005b). Additional long-term effects on postnatal growth, and delays in developmental landmarks (e.g., eye opening, pinna unfolding, surface righting) occur in surviving rat pups at doses greater than the LOAEL. Among the epidemiology studies evaluating the potential associations between PFOS levels during pregnancy and developmental birth outcomes, impacts on growth retardation were observed. Specifically, birth weight deficits were reported in five studies (Apelberg et al. 2007; Chen et al. 2015; Darrow et al. 2013; Maisonet et al. 2012; Washino et al. 2009).

Two animal studies (Lv et al. 2013; Wan et al. 2014) found evidence suggesting that exposure to PFOS during gestation can impact insulin resistance and blood glucose later in life. This identifies women with pregnancy-induced prediabetes as a potential sensitive population. On the basis of results from several animal PFOS studies (Bijland et al. 2011; Wan et al. 2012), another concern is triglyceride (fat) accumulation (steatosis) on the liver for humans receiving a high fat diet.

9 ANALYTICAL METHODS

EPA developed a liquid chromatography/tandem mass spectrometry (LC/MS/MS) analytical method to monitor drinking water for PFASs, including PFOS (Method 537; USEPA 2009c). Accuracy and precision data were generated for PFOS, as well as the other 12 PFASs in reagent water, finished groundwater, and finished surface water. This method is intended for use by analysts skilled in preparing solid phase extractions, operating LC/MS/MS instruments, and interpreting associated data. This method identifies a single-laboratory lowest concentration minimum reporting level or quantitation limit for PFOS at 6.5 ng/L (0.0065 µg/L). The published method detection limit (DL) for PFOS is 1.4 ng/L (0.0014 µg/L).

In this method, PFAS standards, extracts, and samples should not come into contact with any glass containers or pipettes because PFAS can potentially adsorb to the surface of the glassware. Polypropylene containers should be used instead. Also, these compounds can be found in

commonly used laboratory supplies and equipment, such as polytetrafluoroethylene (PTFE) products, liquid chromatograph solvent lines, methanol, aluminum foil, solid phase extraction (SPE) sample transfer lines, and so forth. These materials need to be routinely demonstrated to be free of interferences per the guidelines for laboratory reagent blanks described in the method. As a summary of the method procedure, a preserved 250 mL water sample (fortified with an extraction surrogate) is passed through a SPE cartridge containing polystyrenedivinylbenzene (SDVB) to extract the method analytes and surrogates.

The compounds are eluted from the SPE with a small amount of methanol. The extract is concentrated to dryness with nitrogen in a heated water bath, and then adjusted to a 1 mL volume with 96%:4% (vol/vol) methanol:water after adding the internal standards. The extract is injected into a liquid chromatograph that is interfaced to an MS/MS. The analytes are separated and identified by comparing the acquired mass spectra and retention times to reference spectra and retention times for calibration standards acquired under identical LC/MS/MS conditions. The concentration of each analyte is determined by using the internal standard technique. Surrogate analytes are added to all field and quality control samples to monitor the extraction efficiency of the method analytes. To download *Method 537: Determination of Selected Perfluorinated Alkyl Acids in Drinking Water by Solid Phase Extraction and Liquid Chromatography/Tandem Mass Spectrometry (LC/MS/MS)* (USEPA 2009c), please go to: https://cfpub.epa.gov/si/si_public_file_download.cfm?p_download_id=525468.

10 TREATMENT TECHNOLOGIES

As mentioned above, PFOS is an organic compound in which the carbon-hydrogen bonds are replaced by carbon-fluorine bonds. This influences the chemical characteristics of the molecule and therefore will impact the effectiveness of any given drinking water treatment process. The characteristics of organic contaminants that treatment processes take advantage of include molecular size, solubility, ionic form, volatility, oxidizability, hydrolysis, photolysis, and biodegradability. Because fluorine is the most electronegative element, the carbon-fluorine bond will be one of the strongest bonds in nature, which makes it exceedingly resistant to biodegradation, hydrolysis, oxidation, and photolysis. PFOS is not removed by heating water and can increase in concentration when the water is boiled. Also, because PFOS is a dissolved contaminant that resists being oxidized to an insoluble form, conventional treatment processes designed for particulate control will not be effective. Remaining potentially effective treatment technologies include adsorption, ion exchange resins, and high-pressure membranes. The following subsections discuss the effectiveness of commonly used drinking water technologies in rough order of applicability for PFOS removal. Additional information can be found on EPA's Drinking Water Treatability Database (https://iaspub.epa.gov/tdb/pages/general/home.do) (USEPA 2015b).

To varying degrees, the technologies below can be employed in centralized drinking water facilities, or in a distributed fashion, such as point-of-entry (POE) or point-of-use (POU) applications in buildings and homes. As they imply, POE systems refer to treatment systems that treat the water as it enters the building or house, and POU systems refer to those that treat the water where used, such as a kitchen or bathroom sink. While the cost of treatment varies with scale, the following general discussion on the relative effectiveness of a given technology applies regardless of scale. One reference below specifically addresses POU systems (MDH 2008b).

Activated Carbon Adsorption

Activated carbon is applied in either powdered or granular form. Either can be effective; however, because PFOS has moderate adsorbability, the specifics of the design are very important for achieving successful treatment.

Powdered Activated Carbon

Powdered activated carbon (PAC) is often applied prior to, or within a, conventional treatment train. The contaminant-loaded PAC is then removed, along with the other particulates. Some studies have shown limited PFOS removal in plants using PAC (Quiñones and Snyder 2009). In general, however, PAC can be an effective treatment strategy to remove PFOS given the correct choice of carbon type, the use of high-enough carbon doses, and allowance for adequate contact time (Dudley et al. 2015; Hansen et al. 2010).

Granular Activated Carbon

Granular activated carbon (GAC) is applied as a filtration step either as a filter adsorber, where a relatively short carbon cap is added to an existing sand filter, or as a post-filter adsorber, where a deeper bed is employed as a stand-alone unit following a typical sand filter. Because PFOS has moderate adsorbabality, a post-filter adsorber with a deeper bed is a considered a safer approach. In general, GAC treatment was found to be effective given the correct choice of carbon, adequate bed depth, moderate or low hydraulic loading rate, and frequent replacement or regeneration of the carbon (Appleman et al. 2013, 2014; MDH 2008b; Shivakoti et al. 2010; Takagi et al. 2008).

Membrane Technologies

Many types of membrane technologies exist, broadly classified as either low-pressure or high-pressure systems. This distinction corresponds to the general effectiveness of removing PFOS; low-pressure membranes are ineffective, while high-pressure membranes are effective.

Low-pressure Membranes

Low-pressure systems incorporating cartridge, microfiltration, or ultrafiltration membranes are designed for particulate control. They have relatively large pore structures where water and dissolved contaminants can easily flow, leaving behind the larger particulate matter such as turbidity and microbiological agents. Low-pressure membranes have been found to be ineffective for PFOS control (McLaughlin et al. 2011; Thompson et al. 2011). This is consistent with other treatment processes (e.g., conventional treatment) that target particulate contaminants but not dissolved contaminants. As with conventional treatment, however, low-pressure membranes can be effective if used in conjunction with PAC. The PAC will adsorb the PFOS, and the low-pressure membrane will remove the spent PAC. Care should be taken in the design of such a system to ensure the proper choice of PAC (as mentioned above) (Dudley et al. 2015).

High-pressure Membranes

High-pressure systems have a much tighter pore structure, relying on water diffusion through the membrane material. High-pressure systems such as nanofiltration and reverse osmosis can

reject not only particulates, but also dissolved constituents such as organic contaminants and salts. Reverse osmosis membranes are the tightest of the high-pressure systems, having the ability to reject monovalent salts such as sodium chloride (e.g., sea water desalination). High-pressure membrane systems have been shown to be very effective for PFOS (Appleman et al. 2013, 2014; MDH 2008b; Quiñones and Snyder 2009; Tang et al. 2006, 2007; Thompson et al. 2011).

Ion Exchange Resin Treatment

The two broad categories of ion exchange resins include cationic and anionic. Cationic exchange resins are effective for removing positively charged contaminants. Anion exchange resins are effective for negatively charged contaminants. Because PFOS is negatively charged in drinking waters, cation-exchange resins will not be effective; therefore, they have not been studied. A number of studies have evaluated different anion exchange resins (macroporous styrenedivinylbenzene, gel-type polystyrene divinylbenzene, and polyacrylic quaternary amine resins). Generally, anion exchange resins have been found to be effective for PFOS removal (Appleman et al. 2014; Carter and Farrell 2010; Chularueangaksorn et al. 2013; Dudley et al. 2015), although the design of the system is important. Addressing regenerate brine waste is an important consideration; if frequent regenerations are needed, the amount of operator effort and expertise should also be accounted for in the system design.

Oxidation / Disinfection

Oxidation/disinfection processes can transform certain contaminants into different molecules, which ideally have less toxicity. It can transform certain dissolved constituents into a higher oxidation state that might be less soluble (e.g., iron, manganese). The less soluble form can then be precipitated and removed in the floc or on a media filter of a conventional treatment system. Because of the strength of the carbon-fluorine bond, all drinking water oxidants or disinfectants have been shown to be ineffective in reacting PFOS. This has been shown numerous times for common oxidative/disinfection agents such as packed tower aeration, chloramination, chlorination, ozonation, potassium permanganate, and ultraviolet (UV) treatment (Appleman et al. 2014; Hori et al. 2004; C.S. Liu et al. 2012; McLaughlin et al. 2011; Quiñones and Snyder 2009; Schröder and Meesters 2005; Shivakoti et al. 2010; Thompson et al. 2011). It is likewise true for advanced oxidation processes that used the nonselective hydroxyl radicals as an oxidative agent. Hydroxyl radicals can be produced in many ways, usually by combining technologies such as hydrogen peroxide plus iron (Fenton's reagent), ozone plus peroxide, UV plus titanium dioxide, UV plus ozone, and UV plus peroxide. All of these combinations have been shown to be ineffective for PFOS control at reasonable contact times (Benotti et al. 2009; Hori et al. 2004; Schröder and Meesters 2005; Tellez 2014).

Biological Treatment

Similar to the discussion on oxidation processes, because of the strength of the carbon-fluorine bond, both aerobic and anaerobic biological treatment processes (e.g., biofiltration, bioreactors) are expected to be ineffective for PFOS removal. A number of researchers have found this to be the case (Kwon et al. 2014; Sáez et al. 2008; Thompson et al. 2011). Some results have shown that specific microbes might be able to break the carbon-carbon bonds in

PFOS, albeit slowly; however, this cannot be engineered into a consistent and robust treatment process (Kwon et al. 2014).

Conventional Treatment

Conventional treatment is commonly defined as a series of successive steps (e.g., rapid mix, coagulation, flocculation, sedimentation, and filtration). Certain variations exist, such as direct filtration, which does not employ a sedimentation step. Regardless of the configuration, conventional treatment is designed to remove particulates (e.g., turbidity, microbiological agents). Dissolved contaminants will not be removed by conventional treatment. The exception is when they are oxidized to an insoluble form (e.g., iron, manganese), or if they are exceedingly hydrophobic as evidenced by an extremely low solubility. Therefore, because of the resistance of PFOS to oxidation to an insoluble form, and their moderately high solubility, conventional treatment is not expected to be effective, even at enhanced coagulation conditions. Numerous studies have confirmed this statement (Appleman et al. 2014; Loos et al. 2007; Quinones and Snyder 2009; Shivakoti et al. 2010; Skutlarek et al. 2006; Tabe et al. 2010; Takagi et al. 2008; Thompson et al. 2011; Xiao et al. 2013).

Similar to low-pressure membranes, conventional treatment can be effective if it is used in conjunction with powdered activated carbon (see above). The PAC will adsorb the PFOS and the conventional treatment system will remove the spent PAC in the sedimentation and filtration steps. Care should be taken in the design of such a system to ensure proper choice of PAC, as mentioned above (Dudley et al. 2015).

11 REFERENCES

Abbott, B.D., C.J. Wolf, K.P. Das, R.D. Zehr, J.E. Schmid, A.B. Lindstrom, M.J. Strynar, and C. Lau. 2009. Developmental toxicity of perfluorooctane sulfonate (PFOS) is not dependent of expression of peroxisome proliferator activated receptor-alpha (PPARα) in the mouse. *Reproductive Toxicology* 27:258–265.

ATSDR. (Agency for Toxic Substances and Disease Registry). 2005. *Health Consultation, 3M Chemolite, Perfluorochemical Releases at the 3M – Cottage Grove Facility*. City of Cottage Grove, Washington County, Minnesota. EPA Facility ID: MND006172969, February 18, 2005. Accessed May 2016. http://www.atsdr.cdc.gov/HAC/pha/3M-CGF021805-MN/3M-CGF021805-MN_pt1.pdf.

ATSDR. (Agency for Toxic Substances and Disease Registry). 2015. *Toxicological Profile for Perfluoroalkyls*. Draft for Public Comment. Agency for Toxic Substances and Disease Registry, Public Health Service, United States Department of Health and Human Services, Atlanta, GA. Accessed May 2016. http://www.atsdr.cdc.gov/ToxProfiles/tp200.pdf.

Ahrens, L., M. Shoeib, T. Harner, S.C. Lee, R. Guo, and E.J Reiner. 2011. Wastewater treatment plant and landfills as sources of polyfluoroalkyl compounds to the atmosphere. *Environmental Science & Technology* 45:8098–8105.

Alexander, B.H., G.W. Olsen, J.M. Burris, J.H. Mandel, and J.S. Mandel. 2003. Mortality of employees of a perfluorooctanesulfonyl fluoride manufacturing facility. *Occupational and Environmental Medicine* 60:722–729.

Alexander, B.H., and G.W. Olsen. 2007. Bladder cancer in perfluorooctanesulfonyl fluoride manufacturing workers. *Annals of Epidemiology* 17:471–478.

Andersen, M.E., H.J. Clewell, Y.M. Tan, J.L. Butenhoff, and G.W. Olsen. 2006. Pharmacokinetic modeling of saturable, renal resorption of perfluoroalkylacids in monkeys—probing the determinants of long plasma half-lives. *Toxicology* 227(1):156–164.

Apelberg, B.J., F.R. Witter, J.B. Herbstman, A.M. Calafat, R.U. Halden, L.L. Needham, and L.R. Goldman. 2007. Cord serum concentrations of perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) in relation to weight and size at birth. *Environmental Health Perspectives* 115(11):1670–6.

Appleman, T.D., E.R. Dickenson, C. Bellona, and C.P. Higgins. 2013. Nanofiltration and granular activated carbon treatment of perfluoroalkyl acids. *Journal of Hazardous Materials* 260:740–746.

Appleman, T.D., C.P. Higgins, O. Quinones, B.J. Vanderford, C. Kolstad, J.C. Zeigler-Holady, and E.R. Dickenson. 2014. Treatment of poly-and perfluoroalkyl substances in US full-scale water treatment systems. *Water research* 51:246–255.

Armstrong, D.L., N. Lozano, C.P. Rice, M. Ramirez, and A. Torrents. 2016. Temporal trends of perfluoroalkyl substances in limed biosolids from a large municipal water resource recovery facility. *Journal of Environmental Management* 165:88–95.

Ashby, J., A. Brady, C.R. Elcombe, B.M. Elliot, J. Ishmael, J. Odum, J.D. Tugwood, S. Kettle, and I.F.H. Purchase. 1994. Mechanistically-based human hazard assessment of peroxisome proliferator-induced hepatocarcinogenesis. *Human & Experimental Toxicology* 13(Suppl. 2):S1–S117.

Ashford, R.D. 1994. *Ashford's Dictionary of Industrial Chemicals: Properties, Production, Uses*. Wavelength Publications Ltd.

Bach, C.C., Z. Liew, B.H. Bech, E.A. Nohr, C. Fei, E.C. Bonefeld-Jørgensen, T.B. Henriksen, and J. Olsen. 2015. Perfluoroalkyl acids and time to pregnancy revisited: An update from the Danish National Birth Cohort. *Environmental Health* 14(1):59.

Beesoon, S., and J.W. Martin. 2015. Isomer-specific binding affinity of perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) to serum proteins. *Environmental Science & Technology* 49:5722–5731.

Begley, T.H., K. White, P. Honigfort, M.L. Twaroski, R. Neches, and R.A.Walker. 2005. Perfluorochemicals: potential sources of and migration from food packaging. *Food Additives & Contaminants* 22(10):1023–1031.

Benotti, M.J., B.D. Stanford, E.C. Wert, and S.A. Snyder. 2009. Evaluation of a photocatalytic reactor membrane pilot system for the removal of pharmaceuticals and endocrine disrupting compounds from water. *Water Research* 43(6):1513–1522.

Berg, V., T.H. Nøst, S. Hansen, A. Elverland, A.S. Veyhe, R. Jorde, J.Ø. Odland, and T.M. Sandanger. 2015. Assessing the relationship between perfluoroalkyl substances, thyroid hormones and binding proteins in pregnant women; a longitudinal mixed effects approach. *Environment International* 77:63–69.

Beser, M.I., O. Pardo, J. Beltran, and V. Yusa. 2011. Determination of per- and polyfluorinated substances in airborne particulate matter by microwave-assisted extraction and liquid chromatography–tandem mass spectrometry. *Journal of Chromatography A* 1218:4847–4855.

Bhavsar, S.P., X. Zhang, R. Guo, E. Braekevelt, S. Petro, N. Gandhi, E.J. Reiner, H. Lee, R. Bronsonc, and S.A. Tittlemier. 2014. Cooking fish is not effective in reducing exposure to perfluoroalkyl and polyfluoroalkyl substances. *Environment International* 66:107–114.

Bijland, S., P.C.N. Rensen, E.J. Pieterman, A.C.E. Maas, J.W. van der Hoorn, M.J. van Erk, L.M. Havekes, K.W. van Dijk, S.-C. Chang, E.J. Ehresman, J.L. Butenhoff, and H.M.G. Princen. 2011. Perfluoroalkyl sulfonates cause alkyl chain length-dependent hepatic steatosis and hypolipidemia mainly by impairing lipoprotein production in APOE*3-Leiden CETP mice. *Toxicological Sciences* 123:290–303.

Blaine, A.C., C.D. Rich, E.M. Sedlacko, L.S. Hundal, K. Kumar, C. Lau, M.A. Mills, K.M. Harris, and C.P. Higgins. 2014. Perfluoroalkyl acid distribution in various plant compartments of edible crops grown in biosolids-amended soils. *Environmental Science & Technology* 48:7858−7865.

Bonefeld-Jørgensen, E.C., M. Long, R. Bossi, P. Ayotte, G. Asmund, T. Kruger, M. Ghisari, G. Mulvad, P. Kern, P. Nzulumiki, and E. Dewailly. 2011. Perfluorinated compounds are related to breast cancer risk in Greenlandic Inuit: a case control study. *Environmental Health* 10(1):88.

Bonefeld-Jørgensen, E.C., M. Long, S.O. Fredslund, R. Bossi, and J. Olsen. 2014. Breast cancer risk after exposure to perfluorinated compounds in Danish women: a case-control study nested in the Danish National Birth Cohort. *Cancer Causes Control* 25(11):1439–1448.

Borg, D., J. Bogdanska, M.Sundström, S. Nobel, H. Håkansson, Å. Bergman, J.W. DePierre, K. Halldin, and U. Bergström. 2010. Tissue distribution of 35S-labelled perfluorooctane sulfonate (PFOS) in C57Bl/6 mice following late gestational exposure. *Reproductive Toxicology* 30:550–557.

Boulanger, B., J. Vargo, J.L. Schnoor, and K.C. Hornbuckle. 2004. Detection of perfluorooctane surfactants in Great Lakes water. *Environmental Science & Technology* 38(15):4064–4070.

Buck, R.C., J. Franklin, U. Berger, J.M. Conder, I.T. Cousins, P. de Voogt, A.A. Jensen, K. Kannan, S.A. Mabury, and S.P. van Leeuwen. 2011. Perfluoroalkyl and polyfluoroalkyl substances in the environment: terminology, classification, and origins. *Integrated Environmental Assessment and Management* 7(4):513–541.

Buck Louis, G.M., R. Sundaram, E.F. Schisterman, A.M. Sweeney, C.D. Lynch, R.E. Gore-Langton, J. Maisog, S. Kim, Z. Chen, and D.B. Barr. 2013. Persistent environmental pollutants and couple fecundity: the LIFE study. *Environmental Health Perspectives* 121(2):231–236.

Buck Louis, G.M., Z. Chen, E.F. Schisterman, S. Kim, A.M. Sweeney, R. Sundaram, C.D. Lynch, R.E. Gore-Langton, and D.B. Barr. 2015. Perfluorochemicals and human semen quality: the LIFE study. *Environmental Health Perspectives* 123(1):57–63.

Butenhoff, J.L., D.J. Ehresman, S.-C.Chang, G.A. Parker, and D.G. Stump. 2009. Gestational and lactational exposure to potassium perfluorooctanesulfonate (K+PFOS) in rats: developmental neurotoxicity. *Reproductive Toxicology* 27:319–330.

Butenhoff, J.L., S.C. Chang, G.W. Olsen, and P.J. Thomford. 2012. Chronic dietary toxicity and carcinogenicity study with potassium perfluorooctanesulfonate in Sprague Dawley rats. *Toxicology* 293(1):1–15.

Calafat, A., L.-Y. Wong, K. Zsuzsanna, J.A. Reidy, and L.L. Needham. 2007. Polyfluoroalkyl Chemicals in the U.S. Population: Data from the National Health and Nutrition Examination Survey (NHANES) 2003–2004 and Comparisons with NHANES 1999–2000. *Environmental Health Perspectives* (115):1596–1602.

Cariou, R., B. Veyrand, A. Yamada, A. Berrebi, D. Zalko, S. Durand, C. Pollono, P. Marchand, J.C. Leblanc, J.P. Antignac, and B. Le Bizec. 2015. Perfluoroalkyl acid (PFAA) levels and profiles in breast milk, maternal and cord serum of French women and their newborns. *Environment International* 84:71–81.

Carter, K.E., and J. Farrell. 2010. Removal of perfluorooctane and perfluorobutane sulfonate from water via carbon adsorption and ion exchange. *Separation Science and Technology* 45(6):762–767.

Centers for Disease Control and Prevention (CDC). 2009. *Fourth National Report on Human Exposure to Environmental Chemicals*. Department of Health and Human Services, Centers for Disease Control and Prevention. Accessed May 2016. http://www.cdc.gov/exposurereport/pdf/fourthreport.pdf.

Centers for Disease Control and Prevention (CDC). 2015. *Fourth National Report on Human Exposure to Environmental Chemicals*. Updated Tables, February 2015, Department of Health and Human Services, Centers for Disease Control and Prevention. Accessed May 2016. http://www.cdc.gov/biomonitoring/pdf/FourthReport_UpdatedTables_Feb2015.pdf.

Chan, E., I. Burstyn, N. Cherry, F. Bamforth, and J.W. Martin. 2011. Perfluorinated acids and hypothyroxinemia in pregnant women. *Environmental Research* 111(4):559–564.

Chang, S.-C., J.R. Thibodeaux, M.L. Eastvold, D.J. Ehresman, J.A. Bjork, J.W. Froehlich, C. Lau, R.J. Singh, K.B. Wallace, and J.L. Butenhoff. 2007. Negative bias from analog methods used in the analysis of free thyroxine in rat serum containing perfluorooctanesulfonate (PFOS). *Toxicology* 234:21–33.

Chang, S.-C., J.R. Thibodeaux, M.L. Eastvold, D.J. Ehresman, J.A. Bjork, J.W. Froehlich, C. Lau, R.J. Singh, K.B. Wallace, and J.L. Butenhoff. 2008. Thyroid hormone status and pituitary function in adult rats given oral doses of perfluorooctanesulfonate (PFOS). *Toxicology* 243:330–339.

Chang, S.-C., D.J. Ehresman, J.A. Bjork, K.B. Wallace, G.A. Parker, D.G. Stump, and J. Butenhoff. 2009. Gestational and lactational exposure to potassium perfluorooctanesulfonate (K+PFOS) in rats: toxicokinetics, thyroid hormone status and related gene expression. *Reproductive Toxicology* 27:387–399.

Chang, S.-C., P.E. Noker, G.S. Gorman, S.J. Gibson, J.A. Hart, D.J. Ehresman, and J.L. Butenhoff. 2012. Comparative pharmacokinetics of perfluorooctanesulfonate (PFOS) in rats, mice and monkeys. *Reproductive Toxicology* 33:428–440.

Chang, E.T., H. O. Adami, P. Boffetta, H.J. Wedner, and J.S. Mandel. 2016. A critical review of perfluorooctanoate and perfluorooctanesulfonate exposure and immunological health conditions in humans. *Critical Reviews in Toxicology* 46(4):1–53.

Chen, T., L. Zhang, J-Q. Yue, Z-Q. Lv, W. Xia, Y-J. Wan, Y-Y. Li, and S.-Q. Xu. 2012. Prenatal PFOS exposure induces oxidative stress and apoptosis in the lung of rat off-spring. *Reproductive Toxicology* 33:538–545.

Chen, H., P. He, H. Rao, F. Wang, H. Liu, and J. Yao. 2015. Systematic investigation of the toxic mechanism of PFOA and PFOS on bovine serum albumin by spectroscopic and molecular modeling. *Chemosphere* 129:217–224.

Chularueangaksorn, P., S. Tanaka, S. Fujii, and C. Kunacheva, C. 2013. Regeneration and reusability of anion exchange resin used in perfluorooctane sulfonate removal by batch experiments. *Journal of Applied Polymer Science* 130(2):884–890.

Cifone, M.A. 1999. Unscheduled DNA synthesis in rat liver primary cell cultures with PFOS. Covance study No. 20780-0-447. Covance Laboratories Inc. USEPA AR226-0132.

Cui, L., Q. Zhou, C. Liao, J. Fu, and G. Jiang. 2009. Studies on the toxicological effects of PFOA and PFOS on rats using histological observation and chemical analysis. *Archives of Environmental Contamination and Toxicology* 56:338–349.

Curran, I., S. L. Hierlihy, V. Liston, P. Pantazopoulos, A. Nunnikhoven, S. Tittlemier, M. Barker, K. Trick, and G. Bondy. 2008. Altered fatty acid homeostasis and related toxicologic sequelae in rats exposed to dietary potassium perfluorooctanesulfonate (PFOS). *Journal of Toxicology and Environmental Health, Part A* 71:1526–1541.

D'Alessandro, M.L., D. A. Ellis, J. A. Carter, N.L. Stock, and R.E. March. 2013. Competitive binding of aqueous perfluoroctanesulfonic acid and ibuprofen with bovine serum albumin studied by electrospray ionization mass spectrometry. *International Journal of Mass Spectrometry* 345–347:28–36.

D'Hollander, W., L. Roosens, A. Covaci, C. Cornelis, H. Reynders, K. Van Campenhout, P. de Voogt, and L. Bervoets. 2010. Brominated flame retardants and perfluorinated compounds in indoor dust from homes and offices in Flanders, Belgium. *Chemosphere* 81:478–487.

Danish Ministry of the Environment. 2015. *Perfluoroalkylated substances: PFOA, PFOS and PFOSA: Evaluation of Health Hazards and Proposal of a Health Based Quality Criterion for Drinking Water, Soil and Ground Water*. Environmental project No. 1665, authors: P.B. Larsen and E. Giovalle. Copenhagen, Denmark: The Danish Environmental Protection Agency. Accessed May 2016. http://www2.mst.dk/Udgiv/publications/2015/04/978-87-93283-01-5.pdf.

Darrow, L.A., C.R. Stein, and K. Steenland. 2013. Serum perfluorooctanoic acid and perfluorooctane sulfonate concentrations in relation to birth outcomes in the Mid-Ohio Valley, 2005-2010. *Environmental Health Perspectives* 121(10):1207–1213

Darrow, L.A., P.P. Howards, A. Winquist, and K. Steenland. 2014. PFOA and PFOS serum levels and miscarriage risk. *Epidemiology* 25(4):505–512.

Das, P., V. A. Arias, V. Kambala, M. Mallavarapu, and R. Naidu. 2013. Remediation of Perfluoroctanoate sulfanate in contaminated soil by modified clay absorbant-A risk based approach. *Water, Air, & Soil Pollution* 224:1714.

Das, P., M. Megharaj, and R. Naidu. 2015. Perfluorooctane sulfonate release pattern from soils of fire training areas in Australia and its bioaccumulation potential in the earthworm *Eisenia fetida*. *Environmental Science and Pollution Research* 22(12):8902–8910.

Denys, S., S. Fraize-Frontier, O. Moussa, B. Le Bizec, B. Veyrand, and J.-L. Volatier. 2014. Is the fresh water fish consumption a significant determinant of the internal exposure to perfluoroalkylated substances (PFAS)? *Toxicology Letters* 231:233–238.

Ding, G., J. Zhang, Y. Chen, L. Wang, M. Wang, D. Xiong, and Y. Sun. 2013. Combined effects of PFOS and PFOA on zebrafish (Danio rerio) embryos. *Archives of Environmental Contamination and Toxicology* 64(4):668–675.

DNIPHE (Dutch Institute for Public Health and the Environment). 2010. *Environmental Risk Limits for PFOS: A proposal for Water Quality Standards in Accordance with the Water Framework Directive*. RIVM Report 601714013/2010. Accessed May 2016. http://www.xn--miljdirektoratet-oxb.no/PageFiles/25802/Horing2013-4141_vedlegg.pdf.

DNREC (Delaware Department of Resources and Environmental Control). 2016. *Reporting Level Table*. Accessed May 2016. http://www.dnrec.delaware.gov/dwhs/sirb/Documents/Notification%20Guidance.pdf.

Dong, G.H., Y.H. Zhang, L. Zheng, W. Liu, Y.H. Jin, and Q.C. He. 2009. Chronic effects of perfluorooctanesulfonate exposure on immunotoxicity in adult male C57BL/6 mice. *Archives of Toxicology* 83(9):805–815.

Dong, G.-H., K.-Y. Tung, C.-H. Tsai, M.-M. Liu, D. Wang, W. Liu, Y.-H. Jin, W.S. Hsieh, Y.L. Lee, and P.-C. Chen. 2013. Serum polyfluoroalkyl concentrations, asthma outcomes, and immunological markers in a case-control study of Taiwanese children. *Environmental Health Perspectives* 121(4):507–513.

Dudley, J.T., J. Listgarten, O. Stegle, S.E. Brenner, and L. Parts. 2015. Personalized medicine: from genotypes, molecular phenotypes and the quantified self, towards improved medicine. *Pacific Symposium on Biocomputing* 342–346.

Dudley, L., E.C. Arevalo, and D.R.U. Knappe. 2015. *Removal of Perfluoroalkyl Substances by PAC Adsorption and Anion Exchange*. Web Report #4344, Water Research Foundation.

Egeghy, P., and M. Lorber. 2011. An assessment of the exposure of Americans to perfluorooctane sulfonate: A comparison of estimated intake with values inferred from NHANES data. *Journal of Exposure Science and Environmental Epidemiology* 21:150–168.

Environment Canada. 2006. *Ecological Screening Assessment Report on Perfluorooctane Sulfonate, Its Salts and Its Precursors that Contain the C8F17SO2 or C8F17SO3, or C8F17SO2N Moiety*. Accessed May 2016. http://www.ec.gc.ca/lcpe-cepa/documents/substances/spfo-pfos/ecological_sar_pfos_eng.pdf.

Eriksen, K., M. Sørensen, J.K. McLaughlin, L. Lipworth, A. Tjønneland, K. Overvad, and O. Raaschou-Nielsen, O. 2009. Perfluorooctanoate and perfluorooctanesulfonate plasma levels and risk of cancer in the general Danish population. *Journal of the National Cancer Institute* 101:605–609.

Eriksen, K.T., O. Raaschou-Nielsen, J.K. McLaughlin, L. Lipworth, A. Tjønneland, K. Overvad, and M. Sørensen. 2013. Association between plasma PFOA and PFOS levels and total cholesterol in a middle-aged Danish population. *PLoS ONE* 8:e56969.

European Food Safety Authority (EFSA). 2008. Perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA) and their salts Scientific Opinion of the Panel on Contaminants in the Food chain. *The EFSA Journal* 653:1–131.

EWG (Environmental Working Group). 2015. *National Drinking Water Database*. Accessed May 2016. http://www.ewg.org/tap-water/chemical-contaminants/Perfluorooctane-Sulfonate-PFOS/E206/.

Fasano, M., S. Curry, E. Terreno, M. Galliano, G. Fanali, P. Barciso, S. Notari, and P. Ascenzi. 2005. The extraordinary ligand binding properties of human serum albumin. *IUBMB Life* 57:787–796.

Fei, C., J.K. McLaughlin, R.E. Tarone, and J. Olsen. 2007. Perfluorinated chemicals and fetal growth: a study within the Danish National Birth Cohort. *Environmental Health Perspectives* 115:1677–1682.

Fei, C., J.K. McLaughlin, R. E. Tarone, and J. Olsen. 2008a. Fetal growth indicators and perfluorinated chemicals: a study in the Danish National Birth Cohort. *American Journal of Epidemiology* 168:66–72.

Fei, C., J.K. McLaughlin, L. Lipworth, and J. Olsen. 2008b. Prenatal exposure to perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) and maternally reported developmental milestones in infancy. *Environmental Health Perspectives* 116:1391–1395.

Fei, C., J.K. McLaughlin, L. Lipworth, and J. Olsen. 2009. Maternal levels of perfluorinated chemicals and subfecundity. *Human Reproduction* 1:1–6.

Fei, C., J.K. McLaughlin, L. Lipworth, and J. Olsen. 2010. Prenatal exposure to PFOA and PFOS and risk of hospitalization for infectious diseases in early childhood. *Environmental Research* 110:773–777.

Filipovic, M. 2015. Fate of Perfluoroalkyl Acids in the Aquatic Environment with a Focus on Mass Balance Studies. Ph.D. Stockholm University, Stockholm, Sweden.

Fisher, M., T.E. Arbuckle, M. Wade, and D.A. Haines. 2013. Do perfluoroalkyl substances affect metabolic function and plasma lipids?—analysis of the 2007–2009, Canadian Health Measures Survey (CHMS) Cycle 1. *Environmental Research* 121:95–103.

Fraser, A.J., T.F. Webster, D.J. Watkins, M.J. Strynar, K. Katod, A.M. Calafat, V.M. Vieira, and M.D. McClean. 2013. Polyfluorinated compounds in dust from homes, offices, and vehicles as predictors of concentrations in office workers' serum. *Environment International* 60:128–136.

Frisbee, S.J., A. Shankar, S.S. Knox, K. Steenland, D.A. Savitz, T. Fletcher, and A. Ducatman. 2010. Perfluorooctanoic acid, perfluorooctanesulfonate, and serum lipids in children and adolescents: results from the C8 health project. *Archives of Pediatrics and Adolescent Medicine* 164:860–869.

Fromme, H., M. Schlummer, A. Möller, L. Gruber, G. Wolz, J. Ungewiss, S. Böhmer, W. Dekant, R. Mayer, B. Liebl, and D. Twardella. 2007. Exposure of an adult population to perfluorinated substances using duplicate diet portions and biomonitoring data. *Environmental Science & Technology* 41(22):7928–7933.

Fromme, H., S.A. Tittlemier, W. Völkel, M. Wilhelm, and D. Twardella. 2009. Perfluorinated compounds–exposure assessment for the general population in Western countries. *International Journal of Hygiene and Environmental Health* 212(3):239–270.

Gebbink, W.A., U. Berger, and I.T. Cousins. 2015. Estimating human exposure to PFOS isomers and PFCA homologues: The relative importance of direct and indirect (precursor) exposure. *Environment International* 74:160–169.

German Ministry of Health. 2006. *Assessment of PFOA in the Drinking Water of the German Hochsauerlandkreis*. *Provisional Evaluation of PFT in Drinking Water with the Guide Substances Perfluorooctanoic acid (PFOA) and Perfluorooctane Sulfonate (PFOS) as Examples*. Accessed May 2016. http://www.umweltbundesamt.de/sites/default/files/medien/pdfs/pft-in-drinking-water.pdf.

Gewurtz, S.B., S.P. Bhavsar, S. Petro, C.G. Mahon, X. Zhao, D. Morse, E.J. Reiner, S.A. Tittlemier, E. Braekevelt, and K. Drouillard. 2014. High levels of perfluoroalkyl acids in sport fish species downstream of a firefighting training facility at Hamilton International Airport, Ontario, Canada. *Environment International* 67:1–11.

Gobas, F.A., W. de Wolf, L.P. Burkhard, E. Verbruggen, and K. Plotzke. 2009. Revisiting bioaccumulation criteria for POPs and PBT assessments. *Integrated Environmental Assessment and Management* 5(4):624–637.

Goeden, H., and J. Kelly. 2006. Targeted Sampling 2004-2005. Perfluorochemicals in Minnesota. Minnesota Department of Health.

Goosey, E., and S. Harrad. 2012. Perfluoroalkyl substances in UK indoor and outdoor air: Spatial and seasonal variation, and implications for human exposure. *Environment International* 45:86–90.

Grandjean, P., E.W. Andersen, E. Budtz-Jørgensen, F. Nielsen, K. Mølbak, P. Weihe, and C. Heilmann. 2012. Serum vaccine antibody concentrations in children exposed to perfluorinated compounds. *Journal of the American Medical Association* 307:391–397.

Granum, B., L. S. Haug, E. Namork, S.B. Stølevik, C. Thomsen, I.S. Aaberge, H. van Loveren, M. Løvik, and U.C. Nygaard. 2013. Pre-natal exposure to perfluoroalkyl substances may be associated with altered vaccine antibody levels and immune-related health outcomes in early childhood. *Journal of Immunotoxicology* 10(4):373–379.

Grasty, R.C., B.E. Grey, C.S. Lau, and J.M. Rogers. 2003. Prenatal window of susceptibility to perfluorooctane sulfonate-induced neonatal mortality in the Sprague-Dawley rat. *Birth Defects Research (Part B)* 68:465–471.

Grasty, R.C., J.A. Bjork, K.B. Wallace, D.C. Wolf, C. Lau, and J.M. Rogers. 2005. Effects of prenatal perfluorooctane sulfonate exposure on lung maturation in the perinatal rat. *Birth Defects Research (Part B)* 74:405–416.

Hall, A.P., C.R. Elcombe, J.R. Foster, T. Harada, W. Kaufmann, A. Knippel, K. Küttler, D.E. Malarkey, R.R. Maronpot, A. Nishikawa, T. Nolte, A. Schulte, V. Strauss, and M.J. York. 2012. Liver hypertrophy: a review of adaptive (adverse and non-adverse) changes – conclusions from the 3rd International ESTP Expert Workshop. *Toxicologic Pathology* 40:971–994.

Hamm, M., N.M. Cherry, E. Chan, J. Martin, and I. Burstyn. 2010. Maternal exposure to perfluorinated acids and fetal growth. *Journal of Exposure Science and Environmental Epidemiology* 20(7):589–597.

Hansen, K.J., H.O. Johnson, J.S. Elridge, J.L. Butenhoff, and L.A. Dick. 2002. Quantitative characterization of trace levels of PFOS and PFOA in the Tennessee River. *Environmental Science & Technology* 36(8):1681–1685.

Hansen, M., M, Borresen, M. Schlabach, and G. Cornelissen. 2010. Sorption of perfluorinated compounds from contaminated water to activated carbon. *Journal of Soils and Sediments* 10:179–185.

Harada, K.H., S. Hashida, T. Kaneko, K. Takenaka, M. Minata, K. Inoue, N. Saito, and A. Koizumi. 2007. Biliary excretion and cerebrospinal fluid partition of perfluorooctanoate and perfluorooctane sulfonate in humans. *Environmental Toxicology and Pharmacology* 24(2):134–139.

Hardell, E., A. Kärrman, B. van Bavel, J. Boa, M. Carlberg, and L. Hardell. 2014. Case-control study on perfluorinated alkyl acids (PFAAs) and the risk of prostate cancer. *Environment International* 63:35–39.

Haug, L.S., S. Salihovic, I.E. Jogsten, C. Thomsen, B. van Bavel, G. Lindström, and G. Becher. 2010. Levels in food and beverages and daily intake of perfluorinated compounds in Norway. *Chemosphere* 80(10):1137–1143.

Haug, L.S., S. Huber, G. Becher, and C. Thomsen. 2011. Characterization of human exposure pathways to perfluorinated compounds—comparing exposure estimates with biomarkers of exposure. *Environment International* 37:687–693.

Higgins, C.P., and R.G. Luthy. 2006. Sorption of perfluorinated surfactants on sediments. *Environmental Science & Technology* 40:7251–7256.

Hill, A.B. 1965. The environment and disease: Association or causation? *Proceedings of the Royal Society of Medicine* 58 (5):295–300.

Hlouskova, V., P. Hradkova, J. Poustka, G. Brambilla, S.P. De Filipps, W. D'Hollander, L. Bervoets, D. Herzker, S. Huber, P. De Voogt, and J. Pulkrabova. 2013. Occurrence of perfluoroalkyl substances (PFASs) in various food items of animal origin collected in four European countries. *Food Additives & Contaminants: Part A* 30(11):1918–1932.

Hori, H., E. Hayakawa, N. Yamashita, S. Taniyasu, F. Nakata, and Y. Kobayashi. 2004. High-performance liquid chromatography with conductimetric detection of perfluorocarboxylic acids and perfluorosulfonates. *Chemosphere* 57(4):273–282.

HSDB (Hazardous Substances Data Bank). 2012. TOXNET, Toxicolog Data Network. Accessed May 2016. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB.

Hu, W., P.D. Jones, B.L. Upham, J.E. Trosko, C. Lau, and J.P. Giesy. 2002. Inhibition of gap junctional intercellular communication by perfluorinated compounds in rat liver and dolphin kidney epithelial cell lines in vitro and Sprague-Dawley rats in vivo. *Toxicological Sciences* 68(2):429–436.

Humblet, O., L.G. Diaz-Ramirez, J.R. Balmes, S.M. Pinney, and R.A. Hiatt. 2014. Perfluoroalkyl chemicals and asthma among children 12–19 years of age: NHANES (1999–2008). *Environmental Health Perspectives* 122(10):1129–1133.

Innes, K.E., J.H. Wimsatt, S. Frisbee, and A.M. Ducatman. 2014. Inverse association of colorectal cancer prevalence to serum levels of perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) in a large Appalachian population. *BMC Cancer* 14:45.

Inoue, K., F. Okada, R. Ito, S. Kato, S. Sasaki, S. Nakajima, A. Uno, Y. Saijo, F. Sata, Y. Yoshimura, R. Kishi, and H. Nakazawa. 2004. Perfluorooctane sulfonate (PFOS) and related perfluorinated compounds in human maternal and cord blood samples: assessment of PFOS exposure in a susceptible population during pregnancy. *Environmental Health Perspectives* 112:1204–1207.

Joensen, U.N., R. Bossi, H. Leffers, A.A. Jensen, N.E. Skakkebæk, and N. Jørgensen, N. 2009. Do perfluoroalkyl compounds impair human semen quality? *Environmental Health Perspectives* 117(6):923–927.

Joensen, U.N., B. Veyrand, J.-P. Antignac, M.B. Jensen, J.H. Petersen, P. Marchand, N.E. Skakkebæk, A.-M. Andersson, B. Le Bizec, and N. Jørgensen. 2013. PFOS (perfluorooctanesulfonate) in serum is negatively associated with testosterone levels, but not with semen quality, in healthy men. *Human Reproduction* 28:599–608.

Jogsten, I.E., M. Nadal, B. van Bavel, G. Lindström, and J.L. Domingo. 2012. Per-and polyfluorinated compounds (PFCs) in house dust and indoor air in Catalonia, Spain: implications for human exposure. *Environment International* 39(1):172–180.

Johansson, J.H., U. Berger, R. Vestergren, I.T. Cousins, A. Bignert, A. Glynn, and P.O. Darnerud. 2014. Temporal trends (1999-2010) of perfluoroalkyl acids in commonly consumed food items. *Environmental Pollution* 188:102–108.

Jørgensen, K.T., I.O. Specht, V. Lenters, C.C. Bach, L. Rylander, B.A. Jönsson, C.H. Lindh, A. Giwercman, D. Heederik, G. Toft, and J.P. Bonde. 2014. Perfluoroalkyl substances and time to pregnancy in couples from Greenland, Poland and Ukraine. *Environmental Health* 13(1):116.

Kannan, K., S.H. Yun, and T.J. Evans. 2005. Chlorinated, brominated, and perfluorinated contaminants in livers of polar bears from Alaska. *Environmental Science & Technology* 39(23):9057–9063.

Kärrman, A., J.L. Domingo, X. Llebaria, M. Nadal, E. Bigas, B. van Bavel, and G. Lindström. 2010. Biomonitoring perfluorinated compounds in Catalonia, Spain: concentrations and trends in human liver and milk samples. *Environmental Science and Pollution Research* 17(3):750–758.

Keil, D.E., T. Mehlmann, L. Butterworth, and M.M. Peden-Adams. 2008. Gestational exposure to perfluorooctane sulfonate suppresses immune function in B6C3F1 mice. *Toxicological Sciences* 103(1):77–85.

Kerstner-Wood, C., L. Coward, and G. Gorman. 2003. *Protein Binding of Perfluorohexane Sulfonate, Perfluorooctane Sulfonate and Perfluorooctanoate to Plasma (human, rat, and monkey), and Various Human-Derived Plasma Protein Fractions*. Southern Research Institute. Study ID 9921.7. U.S. Environmental Protection Agency Administrative Record 226-1354.

Kim, S.K., K.T. Lee, C.S. Kang, L. Tao, K. Kannan, K.R. Kim, C.K Kim, J.S. Lee, P.S. Park, Y.W. Yoo, and J.Y. Ha. 2011. Distribution of perfluorochemicals between sera and milk from the same mothers and implications for prenatal and postnatal exposures. *Environmental Pollution* 159(1):169–174.

Knobeloch, L., P. Imm, and H. Anderson. 2012. Perfluoroalkyl chemicals in vacuum cleaner dust from 39 Wisconsin homes. Chemosphere 88(7):779–783.

Konwick, B.J., G.T. Tomy, N. Ismail, J.T. Peterson, R.J. Fauver, D. Higginbotham, and A.T. Fisk. 2008. Concentrations and Patterns of Perfluoroalkyl Acids in Georgia, USA Source Waters Near and Distant to a Major Use Source. *Environmental Toxicology & Chemistry* 27(10):2011–2018.

Kotthoff, M., J. Müller, H. Jürling, M. Schlummer, and D. Fiedler, D. 2015. Perfluoroalkyl and polyfluoroalkyl substances in consumer products. *Environmental Science and Pollution Research* 22(19):14546–14559.

Krippner, J., H. Brunn, S. Falk, S. Georgii, S. Schubert, and T. Stahl. 2014. Effects of chain length and pH on the uptake and distribution of perfluoroalkyl substances in maize (Zea mays). *Chemosphere* 94:85–90.

Kwon, B.G., H.J. Lim, S.H. Na, B.I. Choi, D.S. Shin, and S.Y. Chung. 2014. Biodegradation of perfluorooctanesulfonate (PFOS) as an emerging contaminant. *Chemosphere* 109:221–225.

Langer, V., A. Dreyer, and R. Ebinghaus. 2010. Polyfluorinated compounds in residential and nonresidential indoor air. *Environmental Science & Technology* 44(21):8075–8081.

Lau, C., J.R. Thibodeaux, R.G. Hanson, J.M. Rogers, B.E. Grey, M.E. Stanton, J.L. Butenhoff, and L.A. Stevenson. 2003. Exposure to perfluorooctane sulfonate during pregnancy in rat and mouse. II: postnatal evaluation. *Toxicological Sciences* 74:382–392.

Lewis, R.J. Sr., ed. 2004. *Sax's Dangerous Properties of Industrial Materials*. 11th Edition. Wiley-Interscience, Wiley & Sons, Inc. Hoboken, NJ.

Liao, C., T. Wang, L. Cui, Q. Zhou, S. Duan, and G. Jiang. 2009. Changes in synaptic transmission, calcium current, and neurite growth by perfluorinated compounds are dependent on the chain length and functional group. *Environmental Science & Technology* 43:2099–2104.

Lindstrom, A.B., M.J. Strynar, and E.L. Libelo. 2011a. Polyfluorinated compounds: past, present, and future. *Environmental Science & Technology* 45:7954–7961.

Lindstrom, A.B., M.J. Strynar, A.D. Delinsky, S.F. Makayama, L. McMillan, E.L. Libelo, M. Neill, and L. Thomas. 2011b. Application of WWTP Biosolids and Resulting Perfluorinated Compound Contamination of Surface and Well Water in Decatur, Alabama, USA. *Environmental Science & Technology* 45:8015–8021.

Litton Bionetics, Inc. 1979. *Mutagenicity Evaluation of T-2014 CoC in the Ames Salmonella/Microsome Plate Test*. Final Report. LBI Project No. 20838.

Liu, C.S., K. Shih, and F. Wang. 2012. Oxidative decomposition of perfluorooctane sulfonate in water by permanganate. *Separation and Purification Technology* 87:95–100.

Liu, Y., A. Das, S. Xu, Z. Lin, C. Xu, Z.L. Wang, A. Rohatgi, and C.P. Wong. 2012. Hybridizing ZnO Nanowires with Micropyramid Silicon Wafers as Superhydrophobic High-Efficiency Solar Cells. *Advanced Energy Materials* 2(1):47–51.

Liu, B., H. Zhang, D. Yao, J. Li, L. Xie, X. Wang, Y. Wang, G. Liu, and B. Yang. 2015. Perfluorinated compounds (PFCs) in the atmosphere of Shenzhen, China: Spatial distribution, sources and health risk assessment. *Chemosphere* 138:511–518.

Livsmidelsverket. 2014. Perfluorerade alkylsyror i drickvatten. 2014-02-21. Komplettering, 2014-01-08; Riskhanteringsrapport, 24-03-12, cited in Danish Ministry of the Environment. 2015. *Perfluoroalkylated substances: PFOA, PFOS and PFOSA: Evaluation of health hazards and proposal of a health based quality criterion for drinking water, soil and ground water*. Environmental project No. 1665. Copenhagen, Denmark: The Danish Environmental Protection Agency. Accessed May 2016. http://www2.mst.dk/Udgiv/publications/2015/04/978-87-93283-01-5.pdf.

Long, Y., Y. Wang, G. Ji, L. Yan, F. Hu, and A. Gu. 2013. Neurotoxicity of perfluorooctane sulfonate to hippocampal cells in adult mice. *PLoS ONE* 8:e54176.

Looker, C., M.I. Luster, A.M. Calafat, V.J. Johnson, G.R. Burleson, F.G. Burleson, and T. Fletcher. 2014. Influenza vaccine response in adults exposed to perfluorooctanoate and perfluorooctanesulfonate. *Toxicological Sciences* 138:76–88.

Loos, R., J. Woollgast, T. Huber, and G. Hanke. 2007. Polar herbicides, pharmaceutical products, perfluorooctanesulfonate (PFOS), perfluorooctanoate (PFOA), and nonylphenol and its carboxylates and ethoxylates in surface and tap waters around Lake Maggiore in Northern Italy. *Analytical and Bioanalytical Chemistry* 387:1469.

Lopez-Espinosa, M-J., T. Fletcher, B. Armstron, B. Genser, K. Dhatariya, D. Mondal, A. Ducatman, and G. Leonardi. 2011. Association of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) with age of puberty among children living near a chemical plant. *Environmental Science & Technology* 45(19):8160–8166.

Luebker, D.J., K.J. Hansen, N.M. Bass, J.L. Butenhoff, and A.M. Seacat. 2002. Interactions of fluorochemicals with rat liver fatty acid-binding protein. *Toxicology* 176:175–185.

Luebker, D.J., R.G. York, K.J. Hansen, J.A. Moore, and J.L. Butenhoff. 2005a. Neonatal mortality from in utero exposure to perfluorooctanesulfonate (PFOS) in Sprague-Dawley rats:dose-response and biochemical and pharmacokinetic parameters. *Toxicology* 215:149–169.

Luebker, D.J., M.T. Case, R.G. York, J.A. Moore, K.J. Hansen, and J.L. Butenhoff. 2005b. Two-generation reproduction and cross-foster studies of perfluorooctanesulfonate (PFOS) in rats. *Toxicology* 215:126–148.

Lupton, S.J., J.K. Huwe, D.J. Smith, K.L. Dearfield, and J.J. Johnston. 2014. Distribution and excretion of perfluorooctane sulfonate (PFOS) in beef cattle (Bos taurus). *Environmental Science & Technology* 62:1167–1173.

Lv, Z., G. Li, Y. Li, C. Ying, J. Chen, T. Chen, J. Wei, Y. Lin, Y. Jiang, Y. Wang, B. Shu, B. Xu, and S. Xu. 2013. Glucose and lipid homeostasis in adult rat is impaired by early-life exposure to perfluorooctane sulfonate. *Environmental Toxicology* 28:532–542.

Maisonet, M., M.L. Terrell, M.A. McGeehin, K.Y. Christensen, A. Holmes, A.M. Calafat, and M. Marcus. 2012. Maternal concentrations of polyfluoroalkyl compounds during pregnancy and fetal and postnatal growth in British girls. *Environmental Health Perspectives* 120(10):1432.

Mandel, J., and R. Johnson. 1995. *Mortality Study of Employees at 3M Plant in Decatur, Alabama*. Minneapolis: Division of Environmental and Occupational Health, School of Public Health, University of Minnesota.

Martin, J.W., S.A. Mabury, K.R. Solomon, and D.C. Muir. 2003. Bioconcentration and tissue distribution of perfluorinated acids in rainbow trout (*Oncorhynchus mykiss*). *Environmental Toxicology and Chemistry* 22(1):196–204.

Martin, J.W., M.M. Smithwick, B.M. Braune, P.F. Hoekstra, D.C. Muir, and S.A. Mabury. 2004. Identification of long-chain perfluorinated acids in biota from the Canadian Arctic. *Environmental Science & Technology* 38(2):373–380.

Martin, M.T., R.J. Brennan, W. Hu, E. Ayanoglu, C. Lau, H. Ren, C.R. Wood, J.C. Corton, R.J. Kavlock, and D.J. Dix. 2007. Toxicogenomic study of triazole fungicides and perfluoroalkyl acids in rat livers predict toxicity and categorizes chemicals based on mechanisms of toxicity. *Toxicological Sciences* 97:595–613.

McLaughlin, C.L., S. Blake, T. Hall, M. Harman, R. Kanda, J. Foster, and P.C. Rumsby. 2011. Perfluorooctane sulphonate in raw and drinking water sources in the United Kingdom. *Water and Environment Journal* 25(1):13–21.

MDH (Minnesota Department of Health). 2008a. *Minnesota Fish Eating Advice Tables*. Accessed May 2016. http://www.health.state.mn.us/divs/eh/fish/eating/mealadvicetables.pdf.

MDH (Minnesota Department of Health). 2008b. *Removal of Perfluorochemicals (PFC's) with Point-of-Use (POU) Water Treatment Devices*. Accessed May 2016. http://www.health.state.mn.us/divs/eh/wells/waterquality/poudevicefinal.pdf.

MDH (Minnesota Department of Health). 2009. *Health Risk Limits for Groundwater 2008 Rule Revision*. Accessed May 2016. http://www.health.state.mn.us/divs/eh/risk/guidance/gw/pfos.pdf, Included in Human Health-Based Water Guidance Table. St. Paul, MN: Environmental Health Division, http://www.health.state.mn.us/divs/eh/risk/guidance/gw/table.html.

Mecchi, M.S. 1999. *Salmonella-Eschericia Coli/Mammalian-Microsome Reverse Mutation Assay with PFOS*. Final report. Covance Laboratories. Vienna, VI.

Melzer, D., N. Rice, M.H. Depledge, W.E. Henley, and T.S. Galloway. 2010. Association between serum perfluorooctanoic acid (PFOA) and thyroid disease in the US National Health and Nutrition Examination Survey. *Environmental Health Perspectives* 118:686–92.

Michigan Department of Environmental Quality (MI DEQ). 2013. *Rule 57 Water Quality Values, Surface Water Assessment Section*. Accessed May 2016. http://www.michigan.gov/documents/deq/wrd-swas-rule57_372470_7.pdf.

Mondal, D., R.H. Weldon, B.G. Armstrong, L.J. Gibson, M.J. Lopez-Espinosa, H.M. Shin, and T. Fletcher. 2014. Breastfeeding: a potential excretion route for mothers and implications for infant exposure to perfluoroalkyl acids. *Environmental Health Perspectives* 122(2):187.

Monroy, R., K. Morrison, K. Teo, S. Atkinson, C. Kubwabo, B. Stewart, and W. Foster. 2008. Serum levels of perfluoroalkyl compounds in human maternal and umbilical cord blood samples. *Environmental Research* 108:56–62.

Moody, C.A., J.W. Martin, W.C. Kwan, D.C.G. Muir, and S.A. Mabury. 2002. Monitoring Perfluorinated Surfactants in Biota and Surface Water Samples Following an Accidental Release of Fire-Fighting Foam into Etobicoke Creek. *Environmental Science & Technology* 36(4):545–551.

Moody, C.A., G.N. Hebert, S.H. Strauss, and J.A. Field. 2003. Occurrence and persistence of perfluorooctanesulfonate and other perflourinated surfactants in groundwater at a fire-training area at Wurtsmith Air Force Base, Michigan, USA. *Journal of Environmental Monitoring* 5:341–345.

Murli, H. 1996. *Mutagenicity Test on T-6295 in an In-Vivo Mouse Micronucleus Assay*. Final Report. CHV Study No.: 17403-0-455. Corning Hazelton Inc. (CHV) Vienna, VA.

Murli, H. 1999. *Chromosomal Aberrations in Human Whole Blood Lymphocytes with PFOS*. Final Report. Covance Study No.:2784-0-499. Covance Laboratories Inc., Vienna, VA.

Nakayama, S.F., M.J. Strynar, J.L. Reiner, A.D. Delinsky, and A.B. Lindstrom. 2010. Determination of perfluorinated compounds in the Upper Mississippi River Basin. *Environmental Science & Technology* 44(11):4103–4109.

Nelson, J.W., E.E. Hatch, and T.F. Webster. 2010. Exposure to polyfluoroalkyl chemicals and cholesterol, body weight, and insulin resistance in the general US population. *Environmental Health Perspectives* 118:197–202.

New Jersey Department of Environmental Protection (NJDEP). 2007. D*etermination of Perfluorooctanoic Acid (PFOA) in Aqueous Samples*. Final Report. Jan 2007, NJDEP, Division of Water Supply.

Ngo, H.T., R.B. Hetland, A. Sabaredzovic, L.S. Haug, and I.L. Steffensen. 2014. In utero exposure to asperfluorooctanoate (PFOA) or perfluorooctane sulfonate (PFOS) did not increase body weight or intestinal tumorigenesis in multiple intestinal neoplasia (Min/+) mice. *Environmental Research* 132:251–263.

Noorlander, C.W., S.P. van Leeuwen, J.D. te Biesebeek, M.J. Mengelers, and M.J. Zeilmaker. 2011. Levels of perfluorinated compounds in food and dietary intake of PFOS and PFOA in the Netherlands. *Journal of Agricultural and Food Chemistry* 59(13):7496–7505.

OECD (Organization for Economic Co-operation and Development). 2002. *Hazard Assessment of Perfluorooctane Sulfonate (PFOS) and its Salts*. ENV/JM/Rd(2002)17/FINAL. Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology.

Okada, E., S. Sasaki, Y. Saijo, N. Washino, C. Miyashita, S. Kobayashi, K. Konishi, Y.M. Ito, R. Ito, A. Nakata, Y. Iwasaki, K. Saito, H. Nakazawa, and R. Kishi. 2012. Prenatal exposure to perfluorinated chemicals and relationship with allergies and infectious diseases in infants. *Environmental Research* 112:118–125.

Olsen, G.W., M.M. Burlew, J.M. Burris, and J.H. Mandel. 2001a. *A Cross-Sectional Analysis of Serum Perfluorooctane Sulfonate (PFOS) and Perfluorooctanoate (PFOA) in Relation to Clinical Chemistry, Thyroid Hormone, Hematology and Urinalysis Results from Male and Female Employee Participants of the 2000 Antwerp and Decatur Fluorochemical Medical Surveillance Program*. Final Report. 3M Medical Department. St. Paul, MN.

Olsen, G.W., M.M. Burlew, J.M. Burris, and J.H. Mandel. 2001b. *A Longitudinal Analysis of Serum Perfluorooctane Sulfonate (PFOS) and Perfluorooctanoate (PFOA) Levels in Relation to Lipid and Hepatic Clinical Chemistry Test Results from Male Employee Participants of the 1994/95, 1997 and 2000 Fuorochemical Medical Surveillance Program*. Final Report. 3M Medical Department. St. Paul, MN.

Olsen, G., J.M. Burris, M.M. Burlew, and J.H. Mandel. 2003. Epidemiologic assessment of worker serum perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) concentrations and medical surveillance examinations. *Journal of Occupational and Environmental Medicine* 45:260–270.

Olsen, G.W., J.M. Burris, D.J. Ehresman, J.W. Froehlich, A.M. Seacat, J.L. Butenhoff, and L.R. Zobel. 2007. Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate and perfluorooctanoate in retired fluorochemical production workers. *Environmental Health Perspectives* 115:1298–1305.

Peden-Adams, M.M., J.M. Keller, J.G. EuDaly, J. Berger, G.S. Gilkeson, and D.E. Keil. 2008. Suppression of humoral immunity in mice following exposure to perfluorooctane sulfonate. *Toxicological Sciences* 104:144–154.

Pérez, F., M. Nadal, A. Navarro-Ortega, F. Fàbrega, J.L. Domingo, D. Barceló, and M. Farré. 2013. Accumulation of perfluoroalkyl substances in human tissues. *Environment International* 59:354–362.

Quanrud, D., L. Abrell, R. Arnold, and E. Saez. 2010. *Perflouronated [sic] Compounds in Arizona Groundwater: Sources of Contamination, USGS State Water Resources Research Institute Program*. Accessed May 2016. http://water.usgs.gov/wrri/grant-details.php?ProjectID=2010AZ380B&Year=2010.

Quiñones, O., and S.A. Snyder. 2009. Occurrence of perfluoroalkyl carboxylates and sulfonates in drinking water utilities and related waters from the United States. *Environmental Science & Technology* 43(24):9089–9095.

Rao, M.S., and J.K. Reddy. 1996. Hepatocarcinogenesis of the peroxisome proliferators. *Annals of the New York Academy of Sciences* 804:573.

Raymer, J.H., L.C. Michael, W.B. Studabaker, G.W. Olsen, C.S. Sloan, T. Wilcosky, and D.K. Walmer. 2012. Concentrations of perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) and their associations with human semen quality measurements. *Reproductive Toxicology* 33(4):419–427.

Ren, X.-M., Y.-F. Zhang, L.-H. Guo, Z.-F. Qin, Q.-Y. Lv, and L.-Y. Zhang. 2015. Structure-activity relations in binding of perfluoroalkyl compounds to human thyroid hormone T3 receptor. *Archives of Toxicology* 89:233–242.

Renner, R. 2001. Growing concern over perfluorinated chemicals. *Environmental Science & Technology* 35(7), p.154A–160A.

Renner, R. 2009. EPA finds record PFOS, PFOA levels in Alabama grazing fields. *Environmental Science & Technology* 43(3):1245–1246.

Renzi, M., C. Guerranti, A. Giovani, G. Perra, and S.E. Focardi. 2013. Perfluorinated compounds: Levels, trophic web enrichments and human dietary intakes in transitional water ecosystems. *Marine Pollution Bulletin* 76:146–157.

RIVM (National Institute for Public Health and the Environment). 2010. *Environmental Risk Limits for PFOS: A Proposal for Water Quality Standards in Accordance with the Water Framework Directive*. Report 601714013/2010. Accessed May 2016. http://www.xn--miljdirektoratet-oxb.no/PageFiles/25802/Horing2013-4141_vedlegg.pdf.

Rosen, M.B., J.R. Schmid, J.C. Corton, R.D. Zehr, K.P. Das, B.D. Abbott, and C. Lau. 2010. Gene expression profiling in wild-type and PPARα-null mice exposed to Perfluorooctane sulfonate reveals PPARα-independent effects. *PPAR Research* pii:794739.

Sáez, M., P. de Voogt, and J.R. Parsons. 2008. Persistence of perfluoroalkylated substances in closed bottle tests with municipal sewage sludge. *Environmental Science and Pollution Research* 15(6):472–477.

Schecter, A., J. Colacino, D. Haffner, K. Patel, M. Opel, O. Papke, and L. Birnbaum. 2010. Perfluorinated compounds, Polychlorinated biphenyls, and organochlorine pesticide contamination in composite food Samples from Dallas, Texas, USA. *Environmental Health Perspectives* 118:796–802.

Schröder, H.F., and R.J. Meesters. 2005. Stability of fluorinated surfactants in advanced oxidation processes—a follow up of degradation products using flow injection–mass spectrometry, liquid chromatography–mass spectrometry and liquid chromatography–multiple stage mass spectrometry. *Journal of Chromatography A* 1082(1):110–119.

Seacat, A.M., P.J. Thomford, K.J. Hansen, G.W. Olsen, M.T. Case, and J.L. Butenhoff. 2002. Subchronic toxicity studies on perfluorooctanesulfonate potassium salt in cynomolgus monkeys. *Toxicological Sciences* 68:249–264.

Seacat, A.M., P.J. Thomford, K.J. Hansen, L.A. Clemen, S.R. Eldridge, C.R. Elcombe, and J.L. Butenhoff. 2003. Sub-chronic dietary toxicity of potassium perfluorooctanesulfonate in rats. *Toxicology* 183:117–131.

Seow, J. 2013. *Fire-Fighting Foams with Perfluorochemicals – Environmental Review. Department of Environment and Conservation Western Australia*. Accessed May 2016. http://www.hemmingfire.com/news/fullstory.php/aid/1748/The_final_definitive_version_of__91Fire_Fighting_Foams_with_Perfluorochemicals__96_Environmental_Review_92,_by_Dr_Jimmy_Seow,_Manager,_Pollution_Response_Unit,_Department_of_Environment_and_Conservation_Western_Australia.html.

Shipley, J.M., C.H. Hurst, S.S. Tanaka, F.L. DeRoos, J.L. Butenhoff, A.M. Seacat, and D.J. Waxman. 2004. Trans-activation of PPARα and induction of PPARα target genes by perfluorooctane-based chemicals. *Toxicological Sciences* 80(1):151–160.

Shivakoti, B., S. Fujii, M. Nozoe, S. Tanaka, and C. Kunacheva. 2010. Perfluorinated chemicals (PFCs) in water purification plants (WPPs) with advanced treatment processes. *Water Science and Technology: Water Supply* 10(1):87–95.

Shoeib, M., T. Harner, and P. Vlahos. 2006. Perfluorinated chemicals in the Arctic atmosphere. *Environmental Science & Technology* 40:7577–7583.

Shoeib M., T. Harner, G.M. Webster, and S.C. Lee. 2011. Indoor sources of poly- and perfluorinated compounds (PFCS) in Vancouver, Canada: implications for human exposure. *Environmental Science & Technology* 45(19):7999–8005.

Simmon, V.F. 1978. *In-vitro Microbiological Mutagenicity Assays of 3M Company Compounds T-2247 CoC and T-2248 CoC*. Final Report. SRI Project: LSC-4442-016. SRI International, Menlo Park, CA 94025.

Skutlarek, D., M. Exner, and H. Farber. 2006. Perfluorinated surfactants in surface and drinking waters. *Environmental Science and Pollution Research International* 13(5):299.

Smithwick M., R.J. Norstrom, S.A. Mabury, K. Solomon, T.J. Evans, I. Stirling, M.K. Taylor, and D.C Muir. 2006. Temporal trends of perfluoroalkyl contaminants in polar bears (*Ursus maritimus*) from two locations in the North American Arctic, 1972-2002. *Environmental Science & Technology* 40(4):1139–1143.

Specht, I.O., K.S. Hougaard, M. Spano, D. Bizzaro, G.C. Manicardi, C.H. Lindh, G. Toft, B.A. Jonsson, A. Giwercman, and J.P. Bonde. 2012. Sperm DNA integrity in relation to exposure to environmental perfluoroalkyl substances—a study of spouses of pregnant women in three geographical regions. *Reproductive Toxicology* 33:577–583.

SRC (Syracuse Research Corporation). 2016. *PHYSPROP Database*. Accessed May 2016. http://www.srcinc.com/what-we-do/environmental/scientific-databases.html.

Stahl, L.L., B.D. Snyder, A.R. Olsen, T.M. Kincaid, J.B. Wathen, and H.B. McCarty. 2014. Perfluorinated compounds in fish from U.S. urban rivers and the Great Lakes. *Science of the Total Environment* 499:185–195.

Starkov, A.A., and K.B. Wallace. 2002. Structural determinants of fluorochemical-induced mitochondrial dysfunction. *Toxicological Sciences* 66(2):244–252.

Steenland, K., S. Tinker, S. Frisbee, A. Ducatman, and V. Vaccarino. 2009. Association of perfluorooctanoic acid and perfluorooctane sulfonate with serum lipids among adults living near a chemical plant. *American Journal of Epidemiology* 170:1268–1278.

Stein, C.R., D.A. Savitz, and M. Dougan. 2009. Serum levels of perfluorooctanoic acid and perfluorooctane sulfonate and pregnancy outcome. *American Journal of Epidemiology* 170:837–846.

Stein, C.R., K.J. McGovern, A.M. Pajak, P.J. Maglione, and M.S. Woff. 2015. Perfluoroalkyl and polyfluoroalkyl substances and indicators of immune function in children aged 12-19 y: National Health and Nutrition Examination Survey. *Pediatric Research* 79(2):348–357.

Strynar, M.J., A.B. Lindstrom, S.F. Nakayama, P.P. Egeghy, and L.J. Helfant. 2012. Pilot scale application of a method for the analysis of perfluorinated compounds in surface soils. *Chemosphere* 86:252–257.

Tabe, S., P. Yang, X. Zhao, C. Hao, R. Seth, L. Schweizer, and T. Jamal. 2010. Occurrence and removal of PPCPs and EDCs in the Detroit River watershed. *Water Practice and Technology* 5(1):1–8.

Takacs, M.L., and B.D. Abbott. 2007. Activation of mouse and human peroxisome proliferator-activated receptors (α,β/δ, γ) by perfluorooctanoic acid and perfluorooctane sulfonate. *Toxicological Sciences* 95:108–117.

Takagi, S., F. Adachi, K. Miyano, Y. Koizumi, H. Tanaka, M. Mimura, I. Watanabe, S. Tanabe, and K. Kannan. 2008. Perfluorooctanesulfonate and perfluorooctanoate in raw and treated tap water from Osaka, Japan. *Chemosphere* 72(10):1409–1412.

Tan, F., Y. Jin, W. Liu, X. Quan, J. Chen, and Z. Liang. 2012. Global liver proteome analysis using iTRAQ labeling quantitative proteomic technology to reveal biomarkers in mice exposed to perfluorooctane sulfonate (PFOS). *Environmental Science & Technology* 46:12170–12177.

Tang, C.Y., Q.S. Fu, A.P. Robertson, C.S. Criddle, and J.O. Leckie. 2006. Use of reverse osmosis membranes to remove perfluorooctane sulfonate (PFOS) from semiconductor wastewater. *Environmental Science & Technology* 40(23):7343–7349.

Tang, C.Y., Q.S. Fu, C.S. Criddle, and J.O. Leckie. 2007. Effect of flux (transmembrane pressure) and membrane properties on fouling and rejection of reverse osmosis and nanofiltration membranes treating perfluorooctane sulfonate containing wastewater. *Environmental Science & Technology* 41(6):2008–2014.

Taniyasu, S., K. Kannan, Y. Horii, N. Hanari, and N. Yamashita. 2003. A survey of perfluorooctane sulfonate and related perfluorinated organic compounds in water, fish, birds, and humans from Japan. *Environmental Science & Technology* 37(12):2634–2639.

Tao, L., J. Ma, T. Kunisue, E.L. Libelo, S. Tanabe, and K. Kannan. 2008. Perfluorinated compounds in human breast milk from several Asian countries, and in infant formula and dairy milk from the United States. *Environmental Science & Technology* 42(22):8597–8602.

Tellez, M.H. 2014. Treatment of Perfluorinated Compounds and Nitroaromatics by Photocatalysis in the Presence of Ultraviolet and Solar Light. Master's Thesis, Air Force Institute of Technology, Wright-Patterson Air Force Base, Ohio.

Thibodeaux, J.R., R.G. Hanson, J.M. Rogers, B.E. Grey, B.D. Barbee, J.H. Richards, J.L. Butenhoff, L.A. Stevenson, and C. Lau. 2003. Exposure to perfluorooctane sulfonate during pregnancy in rat and mouse. I: maternal and prenatal evaluations. *Toxicological Sciences* 74:369–381.

Thomford, P.J. 2002. *104-Week Dietary Chronic Toxicity and Carcinogenicity Study with Perfluorooctane Sulfonic Acid Potassium Salt (PFOS; T-6295) in Rats*. Final Report, 3M T-6295 (Covance Study No. 6329-183), Vol. I-IX, 4068 pages, January 2, 2002. 3M, St. Paul, MN.

Thompson, J., L.M.L. Toms, G. Eaglesham, P. Hobson, and J.F. Mueller. 2010. Comparison of PFOS and PFOA serum concentrations in people undergoing regular venesections and in the broader community. *Organohalogen Compounds* 72:826–829.

Thompson, J., G. Eaglesham, J. Reungoat, Y. Poussade, M. Bartkowf, M. Lawrence, and J.F. Mueller. 2011. Removal of PFOS, PFOA and other perfluoroalkyl acids at water reclamation plants in South East Queensland Australia. *Chemosphere* 82:9–17.

Thompson, J., G. Eaglesham, and J. Mueller. 2011. Concentrations of PFOS, PFOA and other perfluorinated alkyl acids in Australian drinking water. *Chemosphere* 83(10):1320–1325.

Tittlemier, S.A., K. Pepper, C. Seymour, J. Moisey, R. Bronson, X-L Cao, and R.W. Dabka. 2007. Dietary exposure of canadians to perfluorinated carboxylates and perfluorooctane sulfonate via consumption of meat, fish, fast foods, and food items prepared in their packaging. *Journal of Agricultural and Food Chemistry* 55(8):3203–3210.

Toft, G., B.A.G. Jönsson, C.H. Lindh, A. Giwercman, M. Spano, D. Heederik, V. Lenters, R. Vermeulen, L. Rylander, H.S. Pedersen, and J.K. Ludwicki. 2012. Exposure to perfluorinated compounds and human semen quality in Arctic and European populations. *Human Reproduction* 27(8):2532–2540.

Tomy, G.T., W. Budakowski, T. Halldorson, P.A. Helm, G.A. Stern, K. Friesen, K. Pepper, S.A. Tittlemier, and A.T. Fisk. 2004. Fluorinated organic compounds in an eastern Arctic marine food web. *Environmental Science & Technology* 38(24):6475–6481.

UK Drinking Water Inspectorate. 2009. *Guidance on the Water Supply (Water Quality) Regulations 20001 Specific to PFOS (perfluorooctane sulphonate) and PFOA (perfluorooctanoic acid) Concentrations in Drinking Water*. SW1A2EY. London, UK. Accessed May 2016. http://www.dwi.gov.uk/stakeholders/information-letters/2009/10_2009annex.pdf.

UNEP (United Nations Environmental Program). 2006. *Report of the Persistent Organic Pollutants Review Committee on the Work of its Second Meeting. Addendum: Risk profile on perfluorooctane sulfonate.* UNEP/POPS/POPRC.2/17/Add.5. http://chm.pops.int/Default.aspx?tabid=2301.

USEPA (U.S. Environmental Protection Agency). 1986. Guidelines for Carcinogen Risk Assessment. EPA/630/R-00/004. *Federal Register* 51(185):33992–34003.

USEPA (U.S. Environmental Protection Agency). 1991. Guidelines for developmental toxicity risk assessment. *Federal Register* 56(234):63798–63826.

USEPA (U.S. Environmental Protection Agency). 1999. *Drinking Water Health Advisories: Pesticides*. Lewis Publishers. Washington, DC.

USEPA (U.S. Environmental Protection Agency). 2000a. *News Releases by Date, EPA and 3M Announce Phase Out of PFOS*. Accessed May 2016. http://yosemite.epa.gov/opa/admpress.nsf/0/33aa946e6cb11f35852568e1005246b4.

USEPA (U.S. Environmental Protection Agency). 2000b. *Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health*. EPA/822/B-00/004. U.S. Environmental Protection Agency, Office of Science and Technology, Office of Water, Washington, DC. http://www.nj.gov/drbc/library/documents/EPA_human-health-criteria2000.pdf.

USEPA (U.S. Environmental Protection Agency). 2002. *A Review of the Reference Dose and Reference Concentration Processes*. EPA/630/P-02/0002F. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC. Accessed May 2016. https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf.

USEPA (U.S. Environmental Protection Agency). 2005a. *Guidelines for Carcinogen Risk Assessment*. EPA/630/P-03/001B. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC. Accessed May 2016. https://www3.epa.gov/airtoxics/cancer_guidelines_final_3-25-05.pdf.

USEPA (U.S. Environmental Protection Agency). 2005b. *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens*. EPA/630/R-03/003F. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC. Accessed May 2016. https://www3.epa.gov/airtoxics/childrens_supplement_final.pdf.

USEPA (U.S. Environmental Protection Agency). 2009a. *Final Contaminant Candidate List 3 Chemicals: Screening to a PCCL*. EPA 815-R-09-007. U.S. Environmental Protection Agency, Office of Water. Accessed May 2016. https://www.epa.gov/sites/production/files/2014-05/documents/ccl3chem_screening_to_pccl_08-31-09_508v2.pdf.

USEPA (U.S. Environmental Protection Agency). 2009b. *Provisional Health Advisories for Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS)*. US Environmental Protection Agency, Office of Water. Washington, DC. Accessed May 2016. https://www.epa.gov/sites/production/files/2015-09/documents/pfoa-pfos-provisional.pdf.

USEPA (U.S. Environmental Protection Agency). 2009c. *Method 537. Determination of Selected Perfluorinated Alkyl Acids in Drinking Water by Solid Phase Extraction and Liquid Chromatography/Tandem Mass Spectrometry (LC/MS/MS)*. EPA/600/R-08/092. U.S. Environmental Protection Agency, National Exposure Research Laboratory, Office of Research and Development. Cincinnati, OH. Accessed May 2016. https://cfpub.epa.gov/si/si_public_file_download.cfm?p_download_id=525468.

USEPA (U.S. Environmental Protection Agency). 2011a. *Perfluorochemical (PFC) Contamination of Biosolids Near Decatur, Alabama (Fact Sheet)*. U.S. Environmental Protection Agency, Washington, DC. Accessed May 2016. https://archive.epa.gov/pesticides/region4/water/documents/web/pdf/epa_decatur_fact_sheet_final.pdf.

USEPA (U.S. Environmental Protection Agency). 2011b. *Exposure Factors Handbook: 2011 Edition (Final)*. EPA/600/R-09/052F. U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment. Washington, DC. Accessed May 2016. https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252.

USEPA (U.S. Environmental Protection Agency). 2014a. *Framework for Human Health Risk Assessment to Inform Decision Making*. EPA/100/R-14/001. U.S. Environmental Protection Agency, Risk Assessment Forum Washington, DC. Accessed May 2016. https://www.epa.gov/sites/production/files/2014-12/documents/hhra-framework-final-2014.pdf.

USEPA (U.S. Environmental Protection Agency). 2014b. *Emerging Contaminants – Perfluorooctane Sulfonate (PFOS) and Perfluorooctanoic Acid (PFOA)*. U.S. Environmental Protection Agency, Solid Waste and Emergency Response. Washington, DC. Accessed May 2016. http://nepis.epa.gov/Exe/ZyPDF.cgi/P100LTG6.PDF?Dockey=P100LTG6.PDF.

USEPA (U.S. Environmental Protection Agency). 2015a. *Draft Contaminant Candidate List 4 (CCL4)*. EPA-505-F-14-001. U.S. Environmental Protection Agency. Washington, DC. Accessed May 2016. https://www.gpo.gov/fdsys/pkg/FR-2015-02-04/pdf/2015-02210.pdf.

USEPA (U.S. Environmental Protection Agency). 2015b. *EPA's Drinking Water Treatability Database*. U.S. Environmental Protection Agency. Washington, DC. Accessed May 2016. https://iaspub.epa.gov/tdb/pages/general/home.do.

USEPA (U.S. Environmental Protection Agency). 2016a. *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)*. EPA 822R16003. U.S. Environmental Protection Agency, Washington, DC. Accessed May 2016. https://www.epa.gov/safewater.

USEPA (U.S. Environmental Protection Agency). 2016b. *Health Effects Support Document for Perfluorooctane Sulfonate (PFOS)*. EPA 822R16002. U.S. Environmental Protection Agency, Washington, DC. Accessed May 2016. https://www.epa.gov/safewater.

USEPA (U.S. Environmental Protection Agency). 2016c. *Drinking Water Health Advisory for Perfluorooctanoic Acid (PFOA)*. EPA 822R16005. U.S. Environmental Protection Agency, Washington, DC. Accessed May 2016. https://www.epa.gov/safewater.

USEPA (U.S. Environmental Protection Agency). 2016d. *Drinking Water Health Advisory for Perfluorooctane Sulfonate (PFOS)*. EPA 822R16004. U.S. Environmental Protection Agency, Washington, DC. Accessed May 2016. https://www.epa.gov/safewater.

USGS (U.S. Geological Survey). 2011. *Report as of FY2011 for 2010MD207B: "Source Characterization of Contamination by Poly- and Per-Fluorinated Chemicals (PFCs) in Maryland Waterways*." Accessed May 2016. http://water.usgs.gov/wrri/10grants/progress/2010MD207B.pdf.

Van Asselt, E.D., R.P.J.J. Rietra, P.F.A.M. Romkens, and H.J. van der Fels-Klerx. 2011. Perfourooctane sulphonate (PFOS) throughout the food production chain. *Food Chemistry* 128:1–6.

Vélez, M.P., T. E. Arbuckle, and W.D. Fraser. 2015. Maternal exposure to perfluorinated chemicals and reduced fecundity: the MIREC study. *Human Reproduction* 30(3):701–709.

Venkatesan, A.K., and R.U. Halden. 2013. National inventory of perfluoroalkyl substances in archived US biosolids from the 2001 EPA National Sewage Sludge Survey. *Journal of Hazardous Materials* 252:413–418.

Vested, A., C. H. Ramlau-Hansen, S.F. Olsen, J.P. Bonde, S.L. Kristensen, T.I. Halldorsson, G. Becher, L.S. Haug, E.H. Ernst, and G. Toft. 2013. Effects of in utero exposure to PFOA and PFOS on human semen quality and hormone profile. *Acta Obstetricia Et Gynecologica Scandinavica* 92:32–32.

Vestergaard, S., F. Nielsen, A.M. Andersson, N.H. Hjøllund, P. Grandjean, H.R. Andersen, and T.K. Jensen. 2012. Association between perfluorinated compounds and time to pregnancy in a prospective cohort of Danish couples attempting to conceive. *Human Reproduction* 27(3):873–880.

Vestergren, R., F. Orata, U. Berger, and I.T. Cousins. 2013. Bioaccumulation of perfluoroalkyl acids in dairy cows in a naturally contaminated environment. *Environmental Science and Pollution Research* 20:7959–7969.

Vierke, L., L. Ahrens, M. Shoeib, E.J. Reiner, R. Guo, W-U Palm, R. Ebinghaus, and T. Harner. 2011. Air concentrations and particle–gas partitioning of polyfluoroalkyl compounds at a wastewater treatment plant. *Environmental Chemistry* 8(4):363–371.

Völkel, W., O. Genzel-Boroviczeny, H. Demmelmair, C. Gebauer, B. Koletzko, D. Twardella, U. Raab, and H. Fromme. 2008. Perfluorooctane sulphonate (PFOS) and perfluorooctanoic acid (PFOA) in human breast milk: results of a pilot study. *International Journal of Hygiene and Environmental Health* 211(3):440–446.

von Ehrenstein, O.S., S.E. Fenton, K. Kato, Z. Kuklenyik, A.M. Calafat, and E.P. Hines. 2009. Polyfluoroalkyl chemicals in the serum and milk of breastfeeding women. *Reproductive Toxicology* 27(3):239–245.

Walters, A., and D. Santillo. 2006. *Uses of Perfluorinated Substances*. GRL-TN-06-2006. Greenpeace Research Laboratories Technical Note 06/2006. Accessed May 2016. http://www.greenpeace.to/publications/uses-of-perfluorinated-chemicals.pdf.

Wambaugh, J.F., R.W. Setzer, A.M. Pitruzzello, J. Liu, D.M. Reif, N.C. Kleinstreuer, N. Ching, Y. Wang, N. Sipes, M. Martin, K. Das, J.C. DeWitt, M. Strynar, R. Judson, K.A. Houck, and C. Lau. 2013. Dosimetric anchoring of in vivo and in vitro studies for perfluorooctanoate and perfluorooctanesulfonate. *Toxicological Sciences* 136:308–327.

Wan, H.T., Y.G. Zhao, X. Wei, K.Y. Hui, J.P. Giesy, and C.K.C. Wong. 2012. PFOS-induced hepatic steatosis, the mechanistic actions on β-oxidation and lipid transport. *Biochimica et Biophysica Acta* 1820:1092–1101.

Wan, H.T., Y.G. Zhao, P.Y. Leung, and C.K.C. Wong. 2014. Perinatal exposure to perfluorooctane sulfonate affects glucose metabolism in adult offspring. *PLoS ONE* 9:e87137.

Wang, S., J. Huang, Y. Yang, Y. Hui, Y. Ge, T. Larssen, G. Yu, S. Deng, B. Wang, and C. Harman. 2013. First report of a Chinese PFOS alternative overlooked for 30 years: its toxicity, persistence, and presence in the environment. *Environmental Science & Technology* 47(18):10163–10170.

Wang, L., Y. Wang, Y. Liang, J. Li, Y. Liu, J. Zhang, A. Zhang, J. Fu, and G. Jiang. 2014. PFOS induced lipid metabolism disturbances in BALB/c mice through inhibition of low density lipoproteins excretion. *Scientific Reports* 4:4582.

Wang, S., Q. Lv, Y. Yang, L.-H. Guo, B. Wan, and L. Zhao. 2014. Cellular target recognition of perfluoroalkyl acids: in vitro evaluation of inhibitory effects on lysine decarboxylase. *Science of the Total Environment* 496:381–388.

Wang, Y., W. Liu, Q. Zhang, H. Zhao, and X. Quan. 2015. Effects of developmental perfluorooctane sulfonate exposure on spatial learning and memory ability of rats and mechanism associated with synaptic plasticity. *Food and Chemical Toxicology* 76:70–76.

Washington J.W., J.J. Ellington, T.M. Jenkins, and M.P. Neill. 2010a. Concentrations, distribution and persistence of fluorotelomer alcohols in sludge-applied soils near Decatur, Alabama, USA. *Environmental Science & Technology* 44:8397–8402.

Washington, J.W., H. Yoo, J.J. Ellington, T.M. Jenkins, and E.L. Libelo. 2010b. Concentrations, distribution and persistence of perfluoroalkylates in sludge-applied soils near Decatur, Alabama, USA. *Environmental Science & Technology* 44:8390–8396.

Washino, N., Y. Saijo, S. Sasaki, S. Kato, S. Ban, K. Koishi, R. Ito, A. Nakata, Y. Iwasaki, K. Saito, H. Nakazawa, and R. Kishi. 2009. Correlations between prenatal exposure to perfluorinated chemicals and reduced fetal growth. *Environmental Health Perspectives* 117:660–667.

Webster, G.M., S.A. Venners, A. Mattman, and J.W. Martin. 2014. Associations between perfluoroalkyl acids (PFASs) and maternal thyroid hormones in early pregnancy: A population-based cohort study. *Environmental Research* 133:338–347.

Webster, G.M., S.A. Rauch, M.N. Ste, A. Mattman, B.P. Lanphear, and S.A. Venners, S.A. 2015. Cross-Sectional Associations of Serum Perfluoroalkyl Acids and Thyroid Hormones in US Adults: Variation According to TPOAb and Iodine Status (NHANES 2007-2008). *Environmental Health Perspectives* EHP1409589.

Weiss, J.M., P.L. Andersson, M.H. Lamoree, P.E.G. Leonards, S.P.J. van Leeuwen, and T. Hamers. 2009. Competitive binding of poly-and perfluorinated compounds to the thyroid hormone transport protein transthyretin. *Toxicological Sciences* 109:206–216.

Wen, L.L., L.Y. Lin, T.C. Su, P.C. Chen, and C.Y. Lin. 2013. Association between serum perfluorinated chemicals and thyroid function in US adults: the National Health and Nutrition Examination Survey 2007–2010. *The Journal of Clinical Endocrinology & Metabolism* 98(9):E1456–E1464.

Whitworth, K.W., L.S. Haug, D.D. Baird, G. Becher, J.A. Hoppin, R. Skjaerven, C. Thomsen, M. Eggesbo, G. Travlos, R. Wilson, and M.P. Longnecker. 2012. Perfluorinated compounds and subfecundity in pregnant women. *Epidemiology* 23(2):257.

Wolf, C.J., M.L. Takacs, J.E. Schmid, C. Lau, and B.D. Abbott. 2008. Activation of mouse and human peroxisome proliferator- activated receptor alpha by perfluoroalkyl acids of different functional groups and chain lengths. *Toxicological Sciences* 106:162–171.

Wolf, C., J. Schmid, C. Lau, and B. Abbott. 2012. Activation of mouse and human peroxisome proliferator- activated receptor-alpha (PPARα) by perfluoroalkyl acids (PFAAs); further investigation of C4-C12 compounds. *Reproductive Toxicology* 33:546–551.

Xiao, F., M.F. Simcik, and J.S. Gulliver. 2013. Mechanisms for removal of perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) from drinking water by conventional and enhanced coagulation. *Water Research* 47:49–56.

Xiao, F., M.F. Simcik, T.R. Halbach, and J.S. Gulliver. 2015. Perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) in soils and groundwater of a US metropolitan area: Migration and implications for human exposure. *Water Research* 72:64–74.

Xie, W., G.D. Bothun, and H.-J. Lehmler. 2010a. Partitioning of perfluorooctanoate into phosphatidylcholine bilayers is chain length-independent. *Chemistry and Physics of Lipids* 163:300–308.

Xie, W., G. Ludewig, K. Wang, and H.-J. Lehmler. 2010b. Model and cell membrane partitioning of perfluorooctanesulfonate is independent of the lipid chain length. *Colloids and Surfaces B: Biointerfaces* 76:128–136.

Xu, Z., S. Fiedler, G. Pfister , B. Henkelmann, C. Mosch, W. Völkel, H. Fromme, and K.-W. Schramm. 2013. Human exposure to fluorotelomer alcohols, perfluorooctane sulfonate and perfluorooctanoate via house dust in Bavaria, Germany. *Science of the Total Environment* 443:485–490.

Yamada, A., N. Bemrah, B. Veyrand, C. Pollono, M. Merlo, V. Desvignes, V. Sirot, M. Oseredczuk, P. Marchand, R. Cariou, and J.P. Antignac. 2014. Perfluoroalkyl Acid Contamination and Polyunsaturated Fatty Acid Composition of French Freshwater and Marine Fishes. *Journal of Agricultural and Food Chemistry* 62(30):7593–7603.

Yamashita, N., K. Kannan, S. Taniyasu, Y. Horii, G. Petrick, and T. Gamo. 2005. A global survey of perfluorinated acids in oceans. *Marine Pollution Bulletin* 51(8):658–668.

Yoo, H., J.W. Washington, T.M. Jenkins, and E.L. Libelo. 2009. Analysis of perfluorinated chemicals in sludge: Method development and initial results. *Journal of Chromatography A* 1216:7831–7839.

Young CJ.., V.I. Furdui, J. Franklin, R.M. Koerner, D.C.G. Muir, and S.A. Mabury. 2007. Perfluorinated acids in arctic snow: new evidence for atmospheric formation. *Environmental Science & Technology* 41(10):3455–3461.

Yu, W.-G., W. Lu, L. Liu, and Y.-H. Jin. 2011. Perfluorooctane sulfonate increased hepatic expression of OAPT2 and MRP2 in rats. *Archives of Toxicology* 85:613–621.

Zareitalabad, P., J. Siemens, M. Hamer, and W. Amelung. 2013. Perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS) in surface waters, sediments, soils and wastewater–a review on concentrations and distribution coefficients. *Chemosphere* 91(6):725–732.

Zhang, X., L. Chen, X.-C. Fei, Y.-S. Ma, and H.-W. Gao. 2009. Binding of PFOS to serum albumin and DNA: insight into the molecular toxicity of perfluorochemicals. *BMC Molecular Biology* 10:16.

Zhang, T., H. Sun, Y. Lin, Y. Qin, X. Geng, and L. Kannan. 2013. Distribution of poly- and perfluoroalkyl substances in matched samples from pregnant women and carbon chain length related maternal transfer. *Environmental Science & Technology* 47:7974–7981.

Zhang, L., Z.-M. Ren, and L.-H. Guo. 2013. Structure-based investigation on the interaction of perfluorinated compounds with human liver fatty acid binding protein. *Environmental Science & Technology* 47:11293–11301.

Zhang, L., X.-M. Ren, B. Wan, and L.-H. Guo. 2014. Structure-dependent binding and activation of perfluorinated compounds on human peroxisome proliferator-activated receptor γ. *Toxicology and Applied Pharmacology* 279:275–283.

Zhang, T., H. Sun, X. Qin, Z. Gan, and K. Kannan. 2014. PFOS and PFOA in paired urine and blood from general adults and pregnant women: assessment of urinary elimination. *Environmental Science and Pollution Research* 22(7):5572–5579.

Zhang, C., R. Sundaram, J. Maisog, A.M. Calafat, D. Boyd Barr, and G.M. Buck Louis. 2015. A prospective study of prepregnancy serum concentrations of perfluorochemicals and the risk of gestational diabetes. *Fertility Sterility* 103:184–189.

Zhao W., J.D. Zitzow, D.J. Ehresman, S.C. Chang, J.L. Butenhoff, J. Forster, and B. Hagenbuch. 2015. Na+/Taurocholate Cotransporting Polypeptide and Apical Sodium-Dependent Bile Acid Transporter Are Involved in the Disposition of Perfluoroalkyl Sulfonates in Humans and Rats. *Toxicological Sciences* 146(2):363–73.

Zheng, L., G.H. Dong, Y.H. Jin, and Q.C. He. 2009. Immunotoxic changes associated with a 7-day oral exposure to perfluorooctanesulfonate (PFOS) in adult male C57BL/6 mice. *Archives of Toxicology* 83(7):679–689.